DOCKET NO.: CRDS-0062 (CRD0931CIP) **PATENT**
Application No.: 10/829,074
Office Action Dated: November 6, 2006

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: **Robert Falotico, et al.**	Confirmation No.: **5950**
Application No.: **10/829,074**	Group Art Unit: **1615**
Filing Date: **April 21, 2004**	Examiner: **Sharon E. Kennedy**

For: **Drug/Drug Delivery Systems for the Prevention and Treatment of Vascular Disease**

ELECTRONICALLY FILED
DATE OF DEPOSIT: January 8, 2007

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

REPLY PURSUANT TO 37 CFR § 1.111

In response to the Official Action dated **November 6, 2006**, reconsideration is respectfully requested in view of the amendments and/or remarks as indicated below:

☐ **Amendments to the Specification** begin on page of this paper.

☒ **Amendments to the Claims** are reflected in the listing of the claims which begins on page 2 of this paper.

☐ **Amendments to the Drawings** begin on page of this paper and include an attached replacement sheet.

☒ **Remarks** begin on page 2 of this paper.

This listing of claims will replace all prior versions, and listings, of claims in the application.

Listing of Claims:

1-14. (canceled)

15. (Previously presented) A drug delivery device comprising: an intraluminal stent; a biocompatible, nonerodible polymeric coating affixed to the intraluminal stent; and rapamycin or a macrocyclic triene analog thereof that binds FKBP12 and is incorporated into the polymeric coating, wherein said device provides an in-stent late loss in diameter at 12 months following implantation in a human of less than about 0.5 mm, as measured by quantitative coronary angiography.

16. (Previously presented) A drug delivery device according to claim 15 that provides an in-stent late loss in diameter at 12 months following implantation in a human of less than about 0.3 mm, as measured by quantitative coronary angiography.

17. (Previously presented) A drug delivery device according to claim 15 or 16 that provides an in-stent diameter stenosis at 12 months following implantation in a human of less than about 22%, as measured by quantitative coronary angiography.

18. (Previously presented) A drug delivery device according to claim 17 that provides an in-stent diameter stenosis at 12 months following implantation in a human of less than about 15%, as measured by quantitative coronary angiography.

19. (Previously presented) A drug delivery device comprising: an intraluminal stent; a biocompatible, nonerodible polymeric coating affixed to the intraluminal stent; and rapamycin or a macrocyclic triene analog thereof that binds FKBP12 incorporated into the polymeric coating, wherein said device provides a mean in-stent late loss in diameter in a human population at 12 months following implantation of less than about 0.5 mm, as measured by quantitative coronary angiography.

20. (Previously presented) A drug delivery device according to claim 19 that provides a mean in-stent late loss in diameter in a human population at 12 months following implantation of less than about 0.3 mm, as measured by quantitative coronary angiography.

21. (Previously presented) A drug delivery device according to claim 19 or 20 that provides a mean in-stent diameter stenosis in a human population at 12 months following implantation of less than about 22%, as measured by quantitative coronary angiography.

22. (Previously presented) A drug delivery device according to claim 21 that provides a mean in-stent diameter stenosis in a human population at 12 months following implantation of less than about 15%, as measured by quantitative coronary angiography.

23. (Previously presented) A method of inhibiting neointimal proliferation in a human coronary artery resulting from percutaneous transluminal coronary angioplasty comprising implanting in the lumen of said coronary artery a drug delivery device comprising: an intraluminal stent; a biocompatible, nonerodible polymeric coating affixed to the intraluminal stent; and rapamycin or a macrocyclic triene analog thereof that binds FKBP12 incorporated into the polymeric coating, wherein said method provides an in-stent late loss in diameter at 12 months following implantation of less than about 0.5 mm, as measured by quantitative coronary angiography.

24. (Previously presented) A method according to claim 23 that provides an in-stent late loss in diameter at 12 months following implantation of less than about 0.3 mm, as measured by quantitative coronary angiography.

25. (Previously presented) A method according to claim 23 or 24 that provides an in-stent diameter stenosis at 12 months following implantation of less than about 22%, as measured by quantitative coronary angiography.

26. (Previously presented) A method according to claim 25 that provides an in-stent diameter stenosis at 12 months following implantation of less than about 15%, as measured by quantitative coronary angiography.

27. (Previously presented) A method of inhibiting neointimal proliferation in a coronary artery resulting from percutaneous transluminal coronary angioplasty comprising implanting in the lumen of said coronary artery a drug delivery device comprising: an intraluminal stent; a biocompatible, nonerodible polymeric coating affixed to the intraluminal stent; and rapamycin or a macrocyclic triene analog thereof that binds FKBP12 incorporated into the polymeric coating, wherein said method provides a mean in-stent late loss in diameter in a human population at 12 months following implantation of less than about 0.5 mm, as measured by quantitative coronary angiography.

28. (Previously presented) A method according to claim 27 that provides a mean in-stent late loss in diameter in a human population at 12 months following implantation of less than about 0.3 mm, as measured by quantitative coronary angiography.

29. (Previously presented) A method according to claim 27 or 28 that provides a mean in-stent diameter stenosis in a human population at 12 months following implantation of less than about 22%, as measured by quantitative coronary angiography.

30. (Previously presented) A method according to claim 29 that provides a mean in-stent diameter stenosis in a human population at 12 months following implantation of less than about 15%, as measured by quantitative coronary angiography.

31. (New) The drug delivery device according to any one of claims 15, 16, 18 or 19 wherein said rapamycin or macrocyclic triene analog thereof is incorporated into the polymeric coating at a dose of from about 64 μg to about 197 μg.

32. (New) The drug delivery device according to claim 31 wherein said rapamycin or macrocyclic triene analog thereof is incorporated into the polymeric coating at a dose of from about 64 μg to about 125 μg.

33. (New) The drug delivery device according to claim 31 that releases a portion of said dose of rapamycin or a macrocyclic triene analog thereof at about six weeks following intraluminal implantation.

34. (New) The drug delivery device according to any one of claims 15, 16, 18 or 19 wherein said rapamycin or macrocyclic triene analog thereof is incorporated into the polymeric coating at a dose of from about 2 μg to about 30 μg per millimeter of stent length.

35. (New) The drug delivery device according to claim 34 wherein said rapamycin or macrocyclic triene analog thereof is incorporated into the polymeric coating at a dose of from about 3 μg to about 13 μg per millimeter of stent length.

36. (New) The drug delivery device according to claim 34 that releases a portion of said dose of rapamycin or a macrocyclic triene analog thereof at about six weeks following intraluminal implantation.

REMARKS

After entry of this amendment, claims 15 to 36 will be pending. No claims are amended or canceled. Dependent claims 31 to 36 are newly added. The dosages recited in new claims 31, 32, 34 and 35 are supported, *inter alia*, by the text and examples provided at page 13, line 25 to page 15, line 11. Support for new claims 33 and 36 may be found throughout the specification, for example at page 17, lines 15 to 17. No new matter is added.

Rejection Under 35 U.S.C. § 112, ¶ 2

The Office Action alleges that claims 15 to 30 are indefinite, and relies on marketing material posted on the Boston Scientific website that is said to teach that "[i]n-stent late loss . . . does not provide any useful information as to the efficiency of a stent delivery device" (Office Action, at 5, last paragraph). Applicants respectfully traverse this rejection.

As an initial matter, Applicants note that the cited website posting is essentially an advertisement, not a peer-reviewed scientific article, whose purpose is to show alleged superiority for Boston Scientific's TAXUS® stent over the CYPHER® stent. Regardless of any bias present in the document, however, it is clear that the Office Action misinterprets and overstates the relevance of this material. The document does not state that in-stent late loss "holds no real value," as asserted in the Office Action (page 6, first paragraph), but that "late loss is an interesting measure" (cited document, at page 3). Although the reference posits that analysis of in-segment late loss provides more complete information than analysis of in-stent late loss, it does not assert that the latter measure is meaningless.

In fact, the reference merely presents a hypothetical (and since refuted) argument as to why in-segment late loss (as measured in terms of risk of either target lesion revascularization (TLR) or angiographic binary restenosis (BAR)) might be a better predictor of efficacy than in-stent late loss. Publications demonstrating the opposite to be true include Mauri, et al.[1], "Relationship of Late Loss in Lumen Diameter to Coronary Restenosis in Sirolimus-Eluting Stents," *Circulation* 2005; 111; 321-327 (enclosed herewith as Exhibit A) which reports on data from the SIRIUS and E-SIRIUS clinical trials (850 and 353 patients, respectively) and

[1] In the interest of full disclosure, Applicants note that two employees of Cordis Corporation, the assignee of the instant application, were co-authors on this article.

concludes that "in-stent late loss was much better correlated with TLR than was in-segment late loss" (*see* page 325, col. 1).

A follow-up study, reported in Mauri, et al., "Late Loss in Lumen Diameter and Binary Restenosis for Drug-Eluting Stent Comparison," *Circulation* 2005; 111; 3435-3442 (enclosed herewith as Exhibit B), further validates the usefulness of in-stent late loss as a predictor of efficacy. As stated in this article, "across the published stent trials, a strong positive association exists between the mean in-stent late loss estimates and binary angiographic restenosis rates" (*see*, p. 3439, col. 2). The article notes that "even small differences in mean in-stent late loss can translate to important differences in binary restenosis" and reports that the findings "support the notion that late loss performance can *reliably predict* the restenosis propensity for new drug-eluting stents." (*See* page 3440, col. 2., emphasis added.)

A third article by Mauri, et al., "Robustness of Late Lumen Loss in Discriminating Drug-Eluting Stents Across Variable Observational and Randomized Trials," *Circulation* 2005; 112; 2833-2839 (enclosed herewith as Exhibit C), goes even further. In this study, the authors demonstrate that "when comparisons are made across separate prospective studies, either randomized or observational, late loss is more reliable than restenosis rates at discriminating the effectiveness of different drug-eluting stents. Thus, "[f]or the practicing physician, in-stent late loss provides a more reliable measure of anti-restenosis propensity than restenosis rates from any given trial source" (*see* page 2837, col. 1).

These peer-reviewed articles, published in a widely respected scientific journal, clearly refute the Office Action's assertion that in-stent late loss is meaningless. To the contrary, the ability of a given stent to provide an in-stent late loss of less than 0.5 mm, and more preferably less than 0.3 mm (as recited in several of the dependent claims) is a strong indicator of that stent's ability to inhibit neointimal proliferation.

In any event, the extent to which late loss serves as a predictor of efficacy is of no moment in assessing whether the instant claims are definite. The test for compliance with the Section 112, ¶ 2 is whether one skilled in the art would understand the metes and bounds of the claim when read in light of the specification. *Union Pac. Res. Co. v. Chesapeake Energy Corp.*, 236 F.3d 684, 692 (Fed. Cir. 2001) (*citing Orthokinetics, Inc. v. Safety Travel Chairs, Inc.*, 806 F.2d 1565, 1576 (Fed. Cir. 1986)). As the Court of Appeals for the Federal Circuit

has stated, a claim is indefinite "if its legal scope is not clear enough that a person of ordinary skill in the art could determine whether a particular [product or method] infringes or not." *Geneva Pharms., Inc. v. GlaxoSmithKline PLC*, 349 F. 3d 1373, 1384 (Fed. Cir. 2003).

The instant claims clearly satisfy this standard. They require, *inter alia*, that the device provide an in-stent late loss in diameter at 12 months following implantation in a human of less than about 0.5 mm, as measured by quantitative coronary angiography. Methods for performing quantitative coronary angiography are well established and readily practiced by those in the art. The point in time at which in-stent late loss is to be determined is also specified in the claim, leaving no ambiguity as to how one would determine whether or not a particular stent meets the limitations of the claims. Applicants respectfully submit, therefore, that the scope of the claims is clearly defined, and that those skilled in the art could readily determine whether a particular device or method is infringing or not.

Accordingly, Applicants respectfully request that the rejection of pending claims 15 to 30 under 35 U.S.C. 112, ¶ 2 be withdrawn.

Rejection Under 35 U.S.C. § 103

Claims 15 to 30 also stand rejected under 35 U.S.C. § 103 as allegedly obvious over U.S. Patent No. 5,288,711 ("Mitchell") in view of U.S. Patent No. 6,355,029 ("Kamath, et al."). Applicants respectfully traverse this rejection because combination of the references' respective teachings (even if motivated) would not have produced any claimed invention.

The Office Action attempts to skirt the issue of whether or not the cited references describes a stent that provides the claimed in-stent late loss by relying on the previously stated arguments regarding alleged indefiniteness of this claim element. As Applicants have shown, however, in-stent late loss is not indefinite. Since the art relied on to make the rejection does not teach or suggest at least this feature, the rejection for alleged obviousness is improper and should be withdrawn.

Rejections Under Doctrine of Obviousness-Type Double Patenting

The Office Action also includes several rejections under the judicially created doctrine of obviousness-type double patenting. However, none of the claims of the pending applications and issued patents that are cited in these rejections include a recitation that the

claimed devices provide an in-stent late loss in diameter at 12 months following implantation in a human of less than about 0.5 mm, as measured by quantitative coronary angiography. Moreover, the Office Action has not demonstrated that this claim element otherwise would have been obvious to those of ordinary skill having knowledge of such claims. Again, basis for the rejection appears to be that the Office Action ascribes no patentable weight to this claim element because it allegedly is indefinite. Because, as noted above, it is not indefinite, Applicants respectfully request that the rejections for alleged obviousness-type double patenting be withdrawn.

CONCLUSION

The foregoing represents a *bona-fide* attempt to address all issues raised in the Office Action dated November 6, 2006. Applicants respectfully submit that the pending claims are in condition for allowance. Accordingly, a Notice of Allowance for all of pending claims 15 to 30 is respectfully requested.

Date: January 8, 2007

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The XIENCE™ V Everolimus Eluting Coronary Stent System
Instructions for Use

℞ ONLY

Table of Contents

1.0 PRODUCT DESCRIPTION

The XIENCE™ V Everolimus Eluting Coronary Stent System (XIENCE V EECSS or XIENCE V stent system) is a device/drug combination product consisting of either the MULTI-LINK VISION® Coronary Stent System or the MULTI-LINK MINI VISION® Coronary Stent System coated with a formulation containing everolimus, the active ingredient, embedded in a non-erodible polymer.

1.1 Device Component Description

The device component consists of the MULTI-LINK MINI VISION or MULTI-LINK VISION stent mounted onto the MULTI-LINK MINI VISION or MULTI-LINK VISION stent delivery system (SDS) respectively. The device component characteristics are summarized in Table 1-1.

Table 1-1: XIENCE V Stent System Product Description

<table>
<tr><th></th><th>XIENCE V Rapid-Exchange (RX) EECSS</th><th>XIENCE V Over-the-Wire (OTW) EECSS</th></tr>
<tr><td>Available Stent Lengths (mm)</td><td colspan="2">8, 12, 15, 18, 23, 28</td></tr>
<tr><td>Available Stent Diameters (mm)</td><td colspan="2">2.5, 2.75, 3.0, 3.5, 4.0</td></tr>
<tr><td>Stent Material</td><td colspan="2">A medical grade L-605 cobalt chromium (CoCr) alloy MULTI-LINK VISION or MULTI-LINK MINI VISION stent</td></tr>
<tr><td>Drug Component</td><td colspan="2">A conformal coating of a non-erodible polymer loaded with 100 µg/cm^2 of everolimus with a maximum nominal drug content of 181 µg on the large stent (4.0 x 28 mm)</td></tr>
<tr><td>Delivery System Working Length</td><td>143 cm</td><td>143 cm</td></tr>
<tr><td>Delivery System Design</td><td>Single access port to inflation lumen. Guide wire exit notch is located 30 cm from tip. Designed for guide wires ≤ 0.014".</td><td>Sidearm adaptor provides access to balloon inflation/deflation lumen and guide wire lumen. Designed for guide wires ≤ 0.014".</td></tr>
<tr><td>Stent Delivery System Balloon</td><td colspan="2">A compliant, tapered balloon, with two radiopaque markers located on the catheter shaft to indicate balloon positioning and expanded stent length.</td></tr>
<tr><td>Balloon Inflation Pressure</td><td colspan="2">Nominal inflation pressure:
8 atm (811 kPa) for 2.5 and 2.75 mm diameters;
9 atm (912 kPa) for 3.0, 3.5, and 4.0 mm diameters
Rated Burst Pressure (RBP): 16 atm (1621 kPa) for all sizes</td></tr>
<tr><td>Guiding Catheter Inner Diameter</td><td colspan="2">≥ 5 F (0.056")</td></tr>
<tr><td>Catheter Shaft Outer Diameter (nominal)</td><td>2.5–3.0 mm / 3.5–4.0 mm
Distal: 0.032" / 0.035"
Proximal: 0.026" / 0.026"</td><td>2.5 mm / 2.75 x 8 – 3.5 x 18 / 3.5 x 23 – 4.0 x 28
Distal: 0.032" / 0.034" / 0.036"
Proximal: 0.042" / 0.042" / 0.042"</td></tr>
</table>

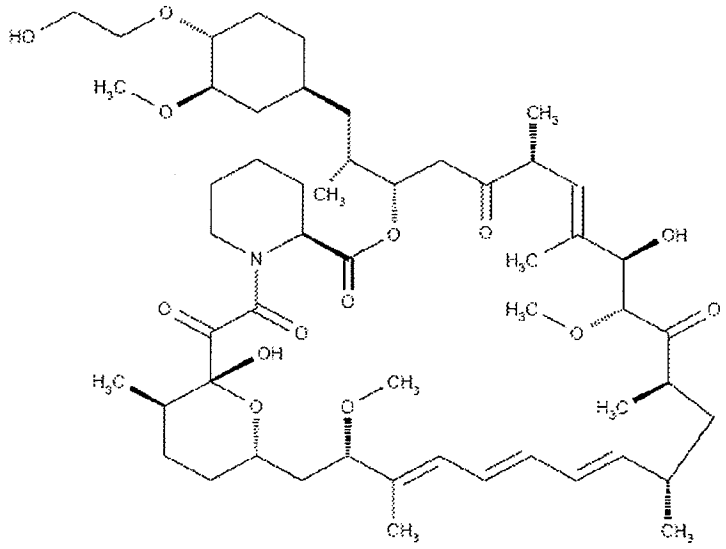
1.2 Drug Component Description

The XIENCE V Everolimus Eluting Coronary Stent (XIENCE V stent) is coated with everolimus (active ingredient), embedded in a non-erodible polymer (inactive ingredient).

1.2.1 Everolimus

Everolimus is the active pharmaceutical ingredient in the XIENCE V stent. It is a novel semi-synthetic macrolide immunosuppressant, synthesized by chemical modification of rapamycin (sirolimus). The everolimus chemical name is 40-O-(2-hydroxyethyl)-rapamycin and the chemical structure is shown in Figure 1-1 below.

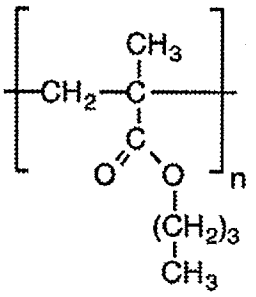
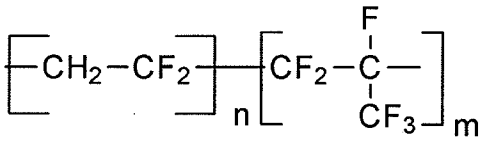
Figure 1-1: Everolimus Chemical Structure



1.2.2. Inactive Ingredients – Non-erodible Polymer

The XIENCE V stent contains inactive ingredients including poly n-butyl methacrylate (PBMA), a polymer that adheres to the stent and drug coating, and PVDF-HFP, which is comprised of vinylidene fluoride and hexafluoropropylene monomers as the drug matrix layer containing everolimus. PBMA is a homopolymer with a molecular weight (Mw) of 264,000 to 376,000 dalton. PVDF-HFP is a non-erodible semi-crystalline random copolymer with a molecular weight (Mw) of 254,000 to 293,000 dalton. The drug matrix copolymer is mixed with everolimus (83%/17% w/w polymer/everolimus ratio) and applied to the entire PBMA coated stent surface. The drug load is 100 $\mu g/cm^2$ for all product sizes. No topcoat layer is used. The polymer chemical structures are shown in Figure 1-2 below.

Figure 1-2: Non-erodible Polymer Chemical Structures

PBMA	PVDF-HFP
	

1.2.3 Product Matrix and Everolimus Content

Table 1-3: XIENCE V EECSS Product Matrix and Everolimus Content

Model Number (RX)	Model Number (OTW)	Nominal Expanded Stent Diameter (mm)	Nominal Unexpanded Stent Length (mm)	Nominal Everolimus Content (μg)
1009539-08	1009545-08	2.5	8	37
1009540-08	1009546-08	2.75	8	37
1009541-08	1009547-08	3.0	8	37
1009542-08	1009548-08	3.5	8	53
1009543-08	1009549-08	4.0	8	53
1009539-12	1009545-12	2.5	12	56
1009540-12	1009546-12	2.75	12	56
1009541-12	1009547-12	3.0	12	56
1009542-12	1009548-12	3.5	12	75
1009543-12	1009549-12	4.0	12	75
1009539-15	1009545-15	2.5	15	75
1009540-15	1009546-15	2.75	15	75
1009541-15	1009547-15	3.0	15	75
1009542-15	1009548-15	3.5	15	98
1009543-15	1009549-15	4.0	15	98
1009539-18	1009545-18	2.5	18	88
1009540-18	1009546-18	2.75	18	88
1009541-18	1009547-18	3.0	18	88
1009542-18	1009548-18	3.5	18	113
1009543-18	1009549-18	4.0	18	113
1009539-23	1009545-23	2.5	23	113
1009540-23	1009546-23	2.75	23	113
1009541-23	1009547-23	3.0	23	113
1009542-23	1009548-23	3.5	23	151
1009543-23	1009549-23	4.0	23	151
1009539-28	1009545-28	2.5	28	132
1009540-28	1009546-28	2.75	28	132
1009541-28	1009547-28	3.0	28	132
1009542-28	1009548-28	3.5	28	181
1009543-28	1009549-28	4.0	28	181

2.0 INDICATIONS

The XIENCE V Everolimus Eluting Coronary Stent System (XIENCE V stent) is indicated for improving coronary luminal diameter in patients with symptomatic heart disease due to *de novo* native coronary artery lesions (length ≤ 28 mm) with reference vessel diameters of 2.5 mm to 4.25 mm.

3.0 CONTRAINDICATIONS

The XIENCE V stent is contraindicated for use in patients:

- Who cannot receive antiplatelet and/or anti-coagulant therapy (see **Section 5.2 Pre- and Post-Procedure Antiplatelet Regimen** for more information)
- With lesions that prevent complete angioplasty balloon inflation or proper placement of the stent or stent delivery system
- With hypersensitivity or contraindication to everolimus or structurally-related compounds, cobalt, chromium, nickel, tungsten, acrylic, and fluoropolymers

4.0 WARNINGS

- Ensure that the inner package sterile barrier has not been opened or damaged prior to use.
- Judicious patient selection is necessary because device use has been associated with stent thrombosis, vascular complications, and/or bleeding events.
- This product should not be used in patients who are not likely to comply with the recommended antiplatelet therapy (see Section 5.2 for important information regarding antiplatelet therapy).

5.0 PRECAUTIONS

5.1 General Precautions

- Stent implantation should only be performed by physicians who have received appropriate training.
- Stent placement should be performed at hospitals where emergency coronary artery bypass graft surgery is accessible.
- Subsequent restenosis may require repeat dilatation of the arterial segment containing the stent. Long-term outcomes following repeat dilatation of the stent is presently unknown.
- Risks and benefits should be considered in patients with severe contrast agent allergies.
- Care should be taken to control the guiding catheter tip during stent delivery, deployment, and balloon withdrawal. Before withdrawing the stent delivery system, visually confirm complete balloon deflation by fluoroscopy to avoid guiding catheter movement into the vessel and subsequent arterial damage.
- Stent thrombosis is a low-frequency event that current drug-eluting stent (DES) clinical trials are not adequately powered to fully characterize. Stent thrombosis is frequently associated with myocardial infarction (MI) or death. Data from the XIENCE V SPIRIT family of trials have been prospectively evaluated and adjudicated using both the protocol definition of stent thrombosis and the definition developed by the Academic

Research Consortium (ARC), and demonstrate specific patterns of stent thrombosis that vary depending on the definition used (see Section 8.2 Stent Thrombosis Definitions and Section 9.4 SPIRIT II and SPIRIT III Pooled Analysis, for more information). In the XIENCE V SPIRIT family of trials analyzed to date, the differences in the incidence of stent thrombosis observed with the XIENCE V stent compared to the TAXUS stent have not been associated with an increased risk of cardiac death, MI, or all-cause mortality. Additional data from longer-term follow-up in the XIENCE V SPIRIT family of trials and analyses of DES-related stent thrombosis are expected and should be considered in making treatment decisions as data become available.

- When DES are used outside the specified Indications for Use, patient outcomes may differ from the results observed in the XIENCE V SPIRIT family of trials.
- Compared to use within the specified Indications for Use, the use of DES in patients and lesions outside of the labeled indications, including more tortuous anatomy, may have an increased risk of adverse events, including stent thrombosis, stent embolization, MI, or death.
- Orally administered everolimus combined with cyclosporine is associated with increased serum cholesterol and triglycerides levels.

5.2 Pre- and Post-Procedure Antiplatelet Regimen

- In XIENCE V SPIRIT FIRST clinical trial, clopidogrel bisulfate or ticlopidine hydrochloride was administered pre-procedure and for a minimum of 3 months post-procedure (75 mg per day). In XIENCE V SPIRIT II and SPIRIT III clinical trials, clopidogrel bisulfate or ticlopidine hydrochloride was administered pre-procedure and for a minimum of 6 months post-procedure (75 mg per day). Aspirin was administered (a minimum of 75 mg per day) pre-procedure and continued for 1 to 5 years (depending on the study). Based on the case report forms from the SPIRIT II and III randomized clinical trials, approximately 92% of patients remained on dual antiplatelet therapy at 6 months and 62% at 1 year See Section 9.0 – Clinical Studies, for more specific information.
- The optimal duration of dual antiplatelet therapy, specifically clopidogrel, is unknown and DES thrombosis may still occur despite continued therapy. Data from several studies on sirolimus-eluting or paclitaxel-eluting stents suggest that a longer duration of clopidogrel than was recommended post-procedurally in DES pivotal trials may be beneficial. Current guidelines recommend that patients receive aspirin indefinitely and that clopidogrel therapy be extended to 12 months in patients at low risk of bleeding (ref: ACC/AHA/SCAI PCI Practice Guidelines[1,2]).
- It is very important that the patient is compliant with the post-procedural antiplatelet therapy recommendations. Early discontinuation of prescribed antiplatelet medication could result in a higher risk of thrombosis, MI, or death. Prior to percutaneous coronary intervention (PCI), if the patient is required to undergo a surgical or dental procedure that might require early discontinuation of antiplatelet therapy, the interventionalist and patient should carefully consider whether a DES and its associated recommended antiplatelet therapy is the appropriate PCI treatment of choice. Following PCI, should a surgical or dental procedure be recommended that requires suspension of antiplatelet therapy, the risks and benefits of the procedure should be weighed against the possible risks associated with early discontinuation of antiplatelet therapy. Patients who require early discontinuation of antiplatelet therapy (e.g., secondary to active bleeding) should

[1] Smith et al. ACC/AHA/SCAI 2005 Guideline Update for Percutaneous Coronary Intervention. JACC, 2006; 47: e1-121

[2] King III et al. 2007 Focused Update of the ACC/AHA/SCAI 2005 Guideline Update for Percutaneous Coronary Intervention. JACC, 2008; 51:172-209

be monitored carefully for cardiac events. At the discretion of the patient's treating physicians, the antiplatelet therapy should be restarted as soon as possible.

5.3 Multiple Stent Use

A patient's exposure to drug and polymer is proportional to the number and total length of implanted stents. In the SPIRIT II and III clinical trials, treatment was limited to 36 mm of total stent length in up to two lesions in different epicardial vessels. Use of more than two stents to treat lesions longer than 28 mm has not been evaluated and may increase patient complication risks. Studies evaluating the effects of higher drug doses have not been conducted.

Effects of multiple stenting using XIENCE V stents combined with other drug-eluting stents are also unknown. When multiple drug-eluting stents are required, use only XIENCE V stents in order to avoid potential interactions with other drug-eluting or coated stents.

In addition, only stents composed of similar materials should be implanted in consecutive stent to stent contact to avoid corrosion potential between unrelated materials. Although *in vitro* tests combining L-605 CoCr alloy with 316 L stainless steel did not increase corrosion potential, these studies have not been conducted *in vivo*.

5.4 Brachytherapy

XIENCE V stent safety and effectiveness has not been evaluated in patients with prior target lesion or in-stent restenosis-related brachytherapy.

5.5 Use in Conjunction with Other Procedures

The safety and effectiveness of using mechanical atherectomy devices (directional atherectomy catheters, rotational atherectomy catheters) or laser angioplasty catheters in conjunction with XIENCE V stent implantation have not been established.

5.6 Use in Special Populations

5.6.1 Pregnancy

Pregnancy Category C. See Section 6.5 – Drug Information, Pregnancy. The XIENCE V stent has not been tested in pregnant women or in men intending to father children. Effects on the developing fetus have not been studied. Effective contraception should be initiated before implanting a XIENCE V stent and continued for one year after implantation. While there is no contraindication, the risks and reproductive effects are unknown at this time.

5.6.2 Lactation

See Section 6.6 – Drug Information, Lactation. A decision should be made whether to discontinue nursing prior to stent implantation considering the importance of the stent to the mother.

5.6.3 Gender

No safety- or effectiveness-related gender differences were observed in the individual XIENCE V clinical trials.

5.6.4 Ethnicity

Insufficient subject numbers prevent ethnicity-related analyses on XIENCE V safety and effectiveness.

5.6.5 Pediatric Use

Safety and effectiveness of the XIENCE V stent in pediatric subjects have not been established.

5.6.6 Geriatric Use

Clinical studies of the XIENCE V stent did not suggest that patients age 65 years and over differed with regard to safety and effectiveness compared to younger patients.

5.7 Lesion/Vessel Characteristics

Safety and effectiveness of the XIENCE V stent have not been established for subject populations with the following clinical settings:

- Unresolved vessel thrombus at the lesion site
- Coronary artery reference vessel diameters < 2.5 mm or > 4.25 mm
- Lesion lengths > 28 mm
- Lesions located in saphenous vein grafts
- Lesions located in unprotected left main coronary artery, ostial lesions, chronic total occlusions, lesions located at a bifurcation
- Previously stented lesions
- Diffuse disease or poor flow (TIMI < 1) distal to the identified lesions
- Excessive tortuosity proximal to or within the lesion
- Recent acute myocardial infarction (AMI) or evidence of thrombus in the target vessel
- Moderate or severe lesion calcification
- Multivessel disease
- In-stent restenosis
- Patients with longer than 24 months follow-up.

5.8 Drug Interactions

See Section 6.3 – Drug Information, Interactions with Drugs or Other Substances.
Several drugs are known to affect everolimus metabolism, and other drug interactions may also occur. Everolimus is known to be a substrate for both cytochrome P4503A4 (CYP3A4) and P-glycoprotein. Everolimus absorption and subsequent elimination may be influenced by drugs that affect these pathways. Everolimus has also been shown to reduce the clearance of some prescription medications when administered orally along with cyclosporine (CsA). Formal drug interaction studies have not been performed with the XIENCE V stent because of limited systemic exposure to everolimus eluted from XIENCE V (see Section 6.2 Pharmacokinetics).

Therefore, due consideration should be given to the potential for both systemic and local drug interactions in the vessel wall when deciding to place the XIENCE V stent in a patient taking a drug with known interaction with everolimus, or when deciding to initiate therapy with such a drug in a patient who has recently received a XIENCE V Stent.

5.9 Immune Suppression Potential

Everolimus, the XIENCE V stent active ingredient, is an immunosuppressive agent. Immune suppression was not observed in the XIENCE V clinical trials. However, for patients who receive several XIENCE V stents simultaneously, it may be possible for everolimus systemic concentrations to approach immunosuppressive levels temporarily, especially in patients who also have hepatic insufficiency or who are taking drugs that inhibit CYP3A4 or P-glycoprotein. Therefore, consideration should be given to patients taking other immunosuppressive agents or who are at risk for immune suppression.

5.10 Lipid Elevation Potential

Oral everolimus use in renal transplant patients was associated with increased serum cholesterol and triglycerides that in some cases required treatment. The effect was seen with both low and high dose prolonged oral therapy in a dose related manner. When used according to the indications for use, exposure to systemic everolimus concentrations from the XIENCE V stent are expected to be significantly lower than concentrations usually obtained in transplant patients. Increased serum cholesterol and triglycerides were not observed in the XIENCE V SPIRIT family of clinical trials.

5.11 Magnetic Resonance Imaging (MRI)

Non-clinical testing has demonstrated that the XIENCE V stent, in single and in overlapped configurations up to 68 mm in length, is MR Conditional. It can be scanned safely under the following conditions:

- Static magnetic field of 1.5 or 3 Tesla
- Spatial gradient field of 720 Gauss/cm or less
- Maximum whole-body-averaged specific absorption rate (SAR) of 2.0 W/kg (normal operating mode) for 15 minutes of scanning or less

The XIENCE V stent should not migrate in this MRI environment. Non-clinical testing at field strengths greater than 3 Tesla has not been performed to evaluate stent migration or heating. MRI at 1.5 or 3 Tesla may be performed immediately following the implantation of the XIENCE V stent.

Stent heating was derived by relating the measured non-clinical, *in vitro* temperature rises in a GE Excite 3 Tesla scanner and in a GE 1.5 Tesla coil to the local specific absorption rates (SARs) in a digitized human heart model. The maximum whole body averaged SAR was determined by validated calculation. At overlapped lengths up to 68 mm, the XIENCE V stent produced a non-clinical maximum local temperature rise of 3°C at a maximum whole body averaged SAR of 2.0 W/kg (normal operating mode) for 15 minutes. These calculations do not take into consideration the cooling effects of blood flow.

The effects of MRI on overlapped stents greater than 68 mm in length or stents with fractured struts are unknown.

As demonstrated in non-clinical testing, an image artifact can be present when scanning the XIENCE V stent. MR image quality may be compromised if the area of interest is in the exact same area, or relatively close to, the position of the XIENCE V stent. Therefore, it may be necessary to optimize the MR imaging parameters for the presence of XIENCE V stents.

5.12 Stent Handling

- **Each stent is for single use only.** Do not resterilize or reuse this device. Note the "use by" (expiration) date on the product label.
- **The foil pouch is not a sterile barrier.** The inner header bag (pouch) within the foil pouch is the sterile barrier. **Only the contents of the inner pouch should be considered sterile. The outside surface of the inner pouch is NOT sterile.**
- **Do not remove the stent from the delivery system.** Removal may damage the stent and/or lead to stent embolization. These components are intended to perform together as a system.
- The delivery system should not be used in conjunction with other stents.
- Special care must be taken not to handle or disrupt the stent on the balloon especially during delivery system removal from packaging, placement over the guide wire and advancement through the rotating hemostatic valve adapter and guiding catheter hub.
- **Do not manipulate, touch, or handle the stent** with your fingers, which may cause coating damage, contamination, or stent dislodgement from the delivery balloon.
- Use only the appropriate balloon inflation media (see Section 13.3.3 – Operator's Instructions, Delivery System Preparation). Do not use air or any gaseous medium to inflate the balloon as this may cause uneven expansion and difficulty in stent deployment.

5.13 Stent Placement

5.13.1 Stent Preparation

- **Do not prepare or pre-inflate the delivery system prior to stent deployment other than as directed.** Use the balloon purging technique described in Section 13.3.3 – Operator's Instructions, Delivery System Preparation.
- **Do not induce negative pressure on the delivery system prior to placing the stent across the lesion.** This may cause dislodgement of the stent from the balloon.
- Use guiding catheters which have lumen sizes that are suitable to accommodate the stent delivery system (see Section 1.1 – Product Description, Device Component Description).

5.13.2 Stent Implantation

- The vessel should be pre-dilated with an appropriate sized balloon. Failure to do so may increase the difficulty of stent placement and cause procedural complications.
- Do not expand the stent if it is not properly positioned in the vessel (see Section 5.14 – Precautions, Stent System Removal).
- Implanting a stent may lead to vessel dissection and acute closure requiring additional intervention (CABG, further dilatation, placement of additional stents, or other).
- Although the safety and effectiveness of treating more than one vessel per coronary artery with XIENCE V stents has not been established, if this is performed, place the

stent in the distal lesion before the proximal lesion in order to minimize dislodgement risk incurred by traversing through deployed stents.

- Stent placement may compromise side branch patency.
- **Do not exceed Rated Burst Pressure (RBP) as indicated on product label.** See Table 14-1, Typical XIENCE V EECSS Compliance. Balloon pressures should be monitored during inflation. Applying pressures higher than specified on the product label may result in a ruptured balloon with possible arterial damage and dissection. The stent inner diameter should approximate 1.1 times the reference diameter of the vessel.
- An unexpanded stent may be retracted into the guiding catheter one time only. An unexpanded stent should not be reintroduced into the artery once it has been pulled back into the guiding catheter. Subsequent movement in and out through the distal end of the guiding catheter should not be performed as the stent may be damaged when retracting the undeployed stent back into the guiding catheter.
- Should **any resistance** be felt **at any time** during coronary stent system withdrawal, the stent delivery system and guiding catheter should be **removed as a single unit** (see Section 5.14 – Precautions, Stent System Removal).
- Stent retrieval methods (i.e., using additional wires, snares, and/or forceps) may result in additional trauma to the coronary vasculature and/or the vascular access site. Complications may include bleeding, hematoma, or pseudoaneurysm.
- Although the stent delivery system balloon is strong enough to expand the stent without rupture, a circumferential balloon tear distal to the stent and prior to complete stent expansion, could cause the balloon to become tethered to the stent, requiring surgical removal. In case of balloon rupture, it should be withdrawn and, if necessary, a new dilatation catheter exchanged over the guide wire to complete the expansion of the stent.
- Ensure the stented area covers the entire lesion/dissection site and that no gaps exist between stents.

5.14 Stent System Removal

Should **any resistance** be felt **at any time** during either lesion access or removing the delivery system post-stent implantation, the stent delivery system and the guiding catheter should be **removed as a single unit.**

When removing the delivery system and guiding catheter as a single unit, the following steps should be executed under direct visualization using fluoroscopy:

- Confirm complete balloon deflation. If unusual resistance is felt during stent delivery system withdrawal, pay particular attention to the guiding catheter position. In some cases it may be necessary to slightly retract the guiding catheter in order to prevent unplanned guiding catheter movement and subsequent vessel damage. In cases where unplanned guiding catheter movement has occurred, a coronary tree angiographic assessment should be undertaken to ensure that there is no damage to the coronary vasculature.
- DO NOT retract the delivery system into the guiding catheter.
- Position the proximal balloon marker just distal to guiding catheter tip.
- Advance the guide wire into the coronary anatomy as far distally as safely possible.
- Tighten the rotating hemostatic valve to secure the delivery system to the guiding catheter, and remove the guiding catheter and delivery system as a **single unit.**

Failure to follow these steps and/or applying excessive force to the delivery system can potentially result in loss or damage to the stent and/or delivery system components.

If it is necessary to retain guide wire position for subsequent artery/lesion access, leave the guide wire in place and remove all other system components.

Stent retrieval methods (i.e., additional wires, snares and/or forceps) may result in additional trauma to the coronary vasculature and/or the vascular access site. Complications may include, but are not limited to, bleeding, hematoma, or pseudoaneurysm.

5.15 Post-Procedure

- When **crossing a newly deployed stent** with an intravascular ultrasound (IVUS) catheter, a coronary guide wire, a balloon catheter or delivery system, exercise care to avoid disrupting the stent placement, apposition, geometry, and/or coating.
- Antiplatelet therapy should be administered post-procedure (see Section 5.2 Pre- and Post-Procedure Antiplatelet Regimen and Section 9.0 Clinical Studies). Patients who require early discontinuation of antiplatelet therapy (e.g., secondary to active bleeding) should be monitored carefully for cardiac events. At the discretion of the patient's treating physician, the antiplatelet therapy should be restarted as soon as possible.
- If the patient requires imaging, see Section 5.11 – Precautions, Magnetic Resonance Imaging (MRI).

6.0 DRUG INFORMATION

6.1 Mechanism of Action

The mechanism by which the XIENCE V Stent inhibits neointimal growth as seen in pre-clinical and clinical studies has not been established. At the cellular level, everolimus inhibits growth factor-stimulated cell proliferation. At the molecular level, everolimus forms a complex with the cytoplasmic protein FKBP-12 (FK 506 Binding Protein). This complex binds to and interferes with FRAP (FKBP-12 Rapamycin Associated Protein), also known as mTOR (mammalian Target Of Rapamycin), leading to inhibition of cell metabolism, growth, and proliferation by arresting the cell cycle at the late G1 stage.

6.2 Pharmacokinetics of the XIENCE V Everolimus Eluting Coronary Stent

Everolimus pharmacokinetics (PK) when eluted from the XIENCE V Stent post-implantation has been evaluated in three different substudies in three different geographies. The SPIRIT III clinical trial design includes a pharmacokinetic substudy in the US randomized arm and a pharmacokinetic substudy in the Japanese non-randomized arm. The third PK substudy was conducted as part of the SPIRIT II clinical trial at sites in Europe, India, and New Zealand. Whole blood everolimus PK parameters determined from subjects receiving the XIENCE V stent are provided in Table 6-1.

Table 6-1: Whole Blood Everolimus Pharmacokinetic Parameters in Patients Following XIENCE V Stent Implantation

	Dose (µg)	t_{max} (h)	C_{max} (ng/mL)	$t_{1/2}$ (h)[a]	AUC_{0-t}[a] (ng.h mL)	$AUC_{0-\infty}$[a] (ng.h/mL)	CL (L/h)[a]
SPIRIT III RCT and 4.0 Arm							
		median (range)	mean ± SD	mean ± SD	mean ± SD	mean ± SD	mean ± SD
2.5-3.0 x 18 mm (n=3[b])	88 µg	0.050 (0.50-1.88)	0.3867 ± 0.09866		5.31 ± 4.114		
3.5-4.0 x 28 mm (n=6[c])	181 µg	0.50 (0.07-1.00)	1.175 ± 0.6817	79.08 ± 57.24	23.73 ± 13.63	44.00 ± 28.67	5.130 ± 2.114
SPIRIT III Japanese Arm							
	Dose (µg)	t_{max} (h)	C_{max} (ng/mL)	$t_{1/2}$ (h)[a]	AUC_{0-t} (ng.h/mL)	$AUC_{0-\infty}$[a] (ng.h/mL)	CL (L/h)
		median (range)	mean ± SD	mean ± SD	mean ± SD	mean ± SD	mean ± SD
2.5-3.0 x 18 mm (n=6)	88 µg	1.00 (0.50-1.02)	0.5017 ± 0.1398	45.22 ± 35.08	5.049 ± 2.138	12.98 ± 7.078	9.286 ± 6.069
3.5-4.0 x 18 mm (n=4[b])	113 µg	0.51 (0.50-0.53)	0.6500 ± 0.08756	53.57 ± 19.34	11.02 ± 4.002	19.97 ± 7.890	6.471 ± 2.807
SPIRIT II Clinical Trial							
	Dose (µg)	t_{max} (h)	C_{max} (ng/mL)	$t_{1/2}$ (h)[a]	AUC_{last} (ng.h/mL)	$AUC_{0-\infty}$[a] (ng.h/mL)	CL (L/h)[a]
		median (range)	mean ± SD	mean ± SD	mean ± SD	mean ± SD	mean ± SD
2.5-3.0 x 18 mm (n=13)	88 µg	0.50 (0.13-2.17)	0.4369 ± 0.1507	54.08 ± 35.78	8.255 ± 5.863	19.60 ± 15.30	8.066 ± 6.443
3.5-4.0 x 18 mm (n=4[c])	113 µg	0.50 (0.50-0.50)	0.5850 ± 0.2630	47.60 ± 62.13	42.54 ± 58.83	22.79 ± 31.47	16.96 ± 13.07
3.5-4.0 x 28 mm (n=4)	181 µg	0.46 (0.17-1.00)	0.7925 ± 0.1406	103.4 ± 64.17	28.07 ± 13.18	52.71 ± 27.40	5.332 ± 5.048

[a] Accurate determination not possible due to rapid disappearance of everolimus from the blood
[b] n= 5 for $t_{1/2}$ and CL
[c] n= 3 for $t_{1/2}$ and CL
t_{max}(h)= time to maximum concentration
C_{max}= maximum observed blood concentration
$t_{1/2}$ (h)= terminal phase half-life
AUC_{0-t} or AUC_{last} = the area beneath the blood concentration versus time curve: time zero to the final quantifiable concentration
$AUC_{(0-\infty)}$ = the area beneath the blood concentration versus time curve: time zero to the extrapolated infinite time
CL= total blood clearance

In all subjects, the maximum time to everolimus disappearance was 168 hours; however, 1 subject in the SPIRIT II clinical trial had detectable levels at 30 days. In all 3 studies, the C_{max} value never reached the minimum therapeutic value of 3.0 ng/mL necessary for effective systemic administration to prevent organ rejection. The PK parameters representing elimination; $t_{½}$, AUC_{0-t}, AUC_{last}, AUC_{∞}, and CL could also not be determined accurately due to rapid everolimus disappearance from blood. These types of results have been seen with other drug-eluting stents.

Everolimus disappearance from circulation following XIENCE V stent implantation should further limit systemic exposure and adverse events associated with long-term systemic administration at therapeutic levels. Despite limited systemic exposure to everolimus, local arterial delivery has been demonstrated in pre-clinical studies.

6.3 Interactions with Drugs or Other Substances

Everolimus is extensively metabolized by the cytochrome P4503A4 (CYP3A4) in the gut wall and liver and is a substrate for the countertransporter P-glycoprotein. Therefore, absorption and subsequent elimination of everolimus may be influenced by drugs that also affect this pathway. Everolimus has also been shown to reduce the clearance of some prescription medications when it was administered orally along with cyclosporine (CsA). Formal drug interaction studies have not been performed with the XIENCE V stent because of limited systemic exposure to everolimus eluted from XIENCE V (see Section 6.2 Pharmacokinetics). However, consideration should be given to the potential for both systemic and local drug interactions in the vessel wall when deciding to place the XIENCE V stent in a subject taking a drug with known interaction with everolimus.

Everolimus, when prescribed as an oral medication, may interact with the drugs/foods[3] listed below. Medications that are strong inhibitors of CYP3A4 might reduce everolimus metabolism *in vivo*. Hence, co-administration of strong inhibitors of CYP3A4 may increase the blood concentrations of everolimus.

- CYP3A4 isozyme inhibitors (ketoconazole, itraconazole, voriconazole, ritonavor, erythromycin, clarithromycin, fluconazole, calcium channel blockers)
- Inducers of CYP3A4 isozyme (rifampin, rifabutin, carbamazepin, phenobarbital, phenytoin)
- Antibiotics (ciprofloxacin, ofloxacin)
- Glucocorticoids
- HMGCoA reductase inhibitors (simvastatin, lovastatin)
- Digoxin
- Cisapride (theoretical potential interaction)
- Sildenafil (Viagra®) (theoretical potential interaction)
- Antihistaminics (terfenadine, astemizole)
- Grapefruit juice

6.4 Carcinogenicity, Genotoxicity, and Reproductive Toxicity

A 26-week carcinogenicity study was conducted to evaluate the carcinogenic potential of XIENCE V stents following subcutaneous implantation in transgenic mice. During the course of the study, there were no abnormal clinical observations that suggested a carcinogenic effect of the test group (XIENCE V stent). The test group did not demonstrate an increased incidence of neoplastic lesions when compared to the negative control group. However, the positive control and the experimental positive control groups demonstrated notable increases in the incidence of neoplastic lesions compared to either the test or the negative control group. Based on the results of this study, the XIENCE V stent does not appear to be carcinogenic when implanted in transgenic mice for 26 weeks.

Genotoxicity studies were conducted on the XIENCE V stent in mammalian cells and bacteria. These studies included gene mutations in bacteria (Ames Test), gene mutations in mammalian cells (chromosomal aberration), test for clastogenicity in mammalian cells, and mammalian erythrocyte micronucleus test. Based on the results of these studies, the XIENCE V stent is not genotoxic.

[3] Certican® Investigator's Brochure. Novartis Pharmaceutical Corporation

In addition, a reproductive toxicity (teratology) study was conducted to demonstrate that implantation of XIENCE V stents in female Sprague-Dawley rats does not affect their fertility or reproductive capability and shows a lack of any reproductive toxicity on their offspring. The XIENCE V stent did not affect the fertility or reproductive capability of female Sprague-Dawley rats. There was no statistical difference between the test article (XIENCE V stent) and the control system in terms of any of the evaluated parameters. The test article had no effect on litter size and caused no increase of in utero mortality. Additionally, the XIENCE V stent did not cause any reproductive toxicity in the offspring in this study.

6.5 Pregnancy

Pregnancy Category C: There are no adequate everolimus or XIENCE V stent related studies in pregnant women. Effects of the XIENCE V stent on prenatal and postnatal rat development were no different than the controls. When administered at oral doses of 0.1 mg/kg or above, everolimus showed effects on prenatal and postnatal rat development limited to slight body weight changes and fetal survival without any specific toxic potential.

Effective contraception should be initiated before implanting a XIENCE V stent and continued for one year post-implantation. The XIENCE V stent should be used in pregnant women only if potential benefits justify potential risks.

Safety of the XIENCE V stent has not been evaluated in males intending to father children.

6.6 Lactation

It is unknown whether everolimus is distributed in human milk. Also, everolimus pharmacokinetic and safety profiles have not been determined in infants. Consequently, mothers should be advised of potential serious adverse reactions to everolimus in nursing infants. Prior to XIENCE V stent implantation, decisions should be made regarding whether to discontinue nursing or conduct an alternate percutaneous coronary intervention procedure.

7.0 OVERVIEW OF CLINICAL STUDIES

Principal XIENCE V safety and effectiveness information is derived from the SPIRIT III clinical trial and is supported by the SPIRIT FIRST and SPIRIT II clinical trials. These studies evaluated XIENCE V EECSS performance in subjects with symptomatic ischemic disease due to *de novo* lesions in native coronary arteries. Major study characteristics are summarized below and listed in Table 7-1.

SPIRIT III, a pivotal clinical trial, was designed to demonstrate the non-inferiority of the XIENCE V stent to the TAXUS EXPRESS^{2}™ Paclitaxel Eluting Coronary Stent System (TAXUS stent) and was conducted in the United States (US) and Japan. The SPIRIT III clinical trial consisted of a US randomized clinical trial (RCT), a non-randomized 4.0 mm diameter stent arm in the US, and a non-randomized arm in Japan, which included a pharmacokinetic substudy (see Section 6.2 Pharmacokinetics of the XIENCE V Everolimus Eluting Coronary Stent). Enrollment is complete in the RCT and the Japan arm.

The SPIRIT III RCT was a prospective, randomized (2:1; XIENCE V:TAXUS), active-controlled, single-blinded, multi-center, clinical trial in the US designed to evaluate the safety and efficacy

of the XIENCE V stent in the treatment of up to two *de novo* lesions ≤ 28 mm in length in native coronary arteries with RVD ≥ 2.5 mm to ≤ 3.75 mm. The RCT study was designed to enroll 1,002 subjects at up to 80 sites in the US. The primary endpoint in the RCT was in-segment late loss at 240 days, and the co-primary endpoint was ischemia-driven target vessel failure (TVF, defined as the composite of cardiac death, MI, or clinically-driven TVR) at 270 days. Other secondary endpoints included clinical outcomes of all the subjects (30, 180, 270 days and annually from 1 to 5 years), as well as angiographic results and intravascular ultrasound (IVUS) results at 240 days. Follow-up through 1 year is currently available, and yearly follow-up for clinical parameters through 5 years is ongoing.

The SPIRIT III 4.0 mm arm was a prospective, multi-center, single-arm registry designed to evaluate the XIENCE V stent in the treatment of up to two *de novo* lesions ≤ 28 mm in length in native coronary arteries with RVD > 3.75 mm to ≤ 4.25 mm. This study was designed to enroll up to 80 subjects at up to 80 sites in the US. Enrolled subjects were scheduled for clinical follow-up at 30, 180, 240, and 270 days and annually from 1 to 5 years, with angiographic follow-up at 240 days. The primary endpoint was in-segment late loss at 240 days compared to the TAXUS arm from the SPIRIT III RCT. Follow-up through 1 year is currently available and yearly follow-up for clinical parameters through 5 years is ongoing.

The SPIRIT III clinical trial included a pharmacokinetic substudy in a subset derived from the RCT[4] and Japan non-randomized arm. Eleven sites in the US and 9 sites in Japan participated in this substudy and have enrolled 34 subjects (17 subjects in the US and 17 subjects in Japan).

The SPIRIT II clinical trial was a randomized, single-blind, active-control, multi-center clinical evaluation. Subject eligibility criteria were similar to the SPIRIT III clinical trial and enrollment duration overlapped between studies. In this study, 300 subjects (3:1 randomization XIENCE V: TAXUS) were enrolled at 28 sites outside the United States. The primary endpoint was in-stent late loss at 6 months. Secondary endpoints included clinical outcomes at 30, 180, 270 days and annually from 1 to 5 years; angiographic results at 180 days and 2 years; and IVUS results at 180 days and 2 years. Clinical follow-up through 2 years is currently available and yearly follow-up for clinical parameters through 5 years is ongoing.

The SPIRIT FIRST clinical trial was a randomized, single-blind, controlled, multi-center first-in-man study. This trial was the first human study to evaluate the XIENCE V stent safety and performance. Sixty subjects [XIENCE V stent (n=28) and MULTI-LINK VISION bare metal control stent (n=32)] were enrolled at 9 sites in Europe. The primary endpoint was in-stent late loss at 6 months on the per-treatment evaluable population, and the major secondary endpoint was the percent in-stent volume obstruction (% VO) at 6 months based on IVUS analysis of the per-treatment evaluable population. Follow-up through 3 years is currently available and yearly follow-up for clinical parameters through 5 years is ongoing.

Table 7-1 summarizes the clinical trial designs for the SPIRIT family of trials.

[4] Includes one subject from the 4.0 mm non-randomized arm

Table 7-1: XIENCE V SPIRIT Clinical Trial Designs

	SPIRIT III clinical trial		SPIRIT II clinical trial	SPIRIT FIRST clinical trial
	RCT	Registries		
Study Type/Design	• Multi-center • Randomized • Single-blinded • Active-Control	• Multi-center • Single-arm • Open-label	• Multi-center • Randomized • Single-blinded • Active-Control	• Multi-center • Randomized • Single-blinded • Control
Number of Subjects Enrolled	Total: 1,002 XIENCE V: 668 TAXUS Control: 334	Total: 168 4.0 mm: 80 Japan: 88*	Total: 300 XIENCE V: 225 TAXUS Control: 75	Total: 60 XIENCE V: 30 VISION Control: 30
Treatment	Up to two *de novo* lesions in different epicardial vessels	Up to two *de novo* lesions in different epicardial vessels	Up to two *de novo* lesions in different epicardial vessels	Single *de novo* lesion
Lesion Size	RVD: ≥ 2.5 ≤ 3.75 mm Length: ≤ 28 mm	4.0 mm RVD: > 3.75 ≤ 4.25 mm Length: ≤ 28 mm	RVD: ≥ 2.5 ≤ 4.25 mm Length: ≤ 28 mm	RVD: 3 mm Length: ≤ 12 mm
		Japan RVD: ≥ 2.5 ≤ 4.25 mm Length: ≤ 28 mm		
Stent Sizes (XIENCE V)	Diameter: 2.5, 3.0, 3.5 mm Length: 8, 18, 28 mm	4.0 mm Diameter: 4.0 mm Length: 8, 18, 28 mm Japan Diameter: 2.5, 3.0, 3.5, 4.0 mm Length: 8, 18, 28 mm	Diameter: 2.5, 3.0, 3.5, 4.0 mm Length: 8, 18, 28 mm	Diameter: 3.0 mm Length: 18 mm
Post-procedure Antiplatelet Therapy	Clopidogrel 6 months minimum (or ticlopidine per site standard), Aspirin 5 years	4.0 mm: same as RCT Japan: Ticlopidine 3 months, Aspirin 5 years	Clopidogrel 6 months minimum (or ticlopidine per site standard), Aspirin 1 year	Clopidogrel 3 months minimum (or ticlopidine per site standard), Aspirin 1 year
Primary Endpoint	In-segment late loss at 240-days	In-segment late loss at 240-days	In-stent late loss at 180-days	In-stent late loss at 180-days
Co-Primary Endpoint	TVF at 270-days	None	None	None
Clinical Follow-up	30, 180, 240, 270 days, 1 to 5 years	30, 180, 240, 270 days, 1 to 5 years	30, 180, 270 days, 1 to 5 years	30, 180, 270 days, 1 to 5 years
Angiographic Follow-up	240 days (N=564)	240 days (All registry)	180-day (all), 2-years (N=152)	180-days, 1-year (all)
IVUS Follow-up	240 days (N=240)	240 days (Japan only)	180-day, 2-years (N=152)	180-days, 1-year (all)
PK Study	US: Minimum 15 subjects with single lesion, maximum 20 with dual lesions Japan: Minimum 10 subjects with single lesion, maximum 20 with dual lesions		Minimum 15 subjects with single lesion, maximum 20 with dual lesions	None
Status	One year reported; 2, 3, 4 and 5 years planned		One and 2 years reported; 3, 4 and 5 years planned	One, 2, and 3 years reported; 4 and 5 years planned

*Only pharmacokinetic substudy results included (see Section 6.2 Pharmacokinetics of the XIENCE V Everolimus Eluting Coronary Stent).

8.0 ADVERSE EVENTS

8.1 Observed Adverse Events

Principal adverse event information is derived from SPIRIT III, SPIRIT II and SPIRIT FIRST clinical trials and is shown in Table 8.1-1 and 8.1-2. Within these tables, the Intent-to-Treat population includes all subjects randomized, while the Per-Treatment Evaluable population includes only those subjects who received a study device at the target lesion with no major procedure protocol deviations except deviations relating to the treatment arm, for whom follow-up data are available. See also Section 8.3 – Adverse Events, Potential Adverse Events. See Section 9.0 – Clinical Studies for more complete study design descriptions and results.

Table 8.1-1: SPIRIT III, II and FIRST:
Principal Adverse Events From Post-Procedure to 1 Year

	SPIRIT III			SPIRIT II		SPIRIT FIRST	
	XIENCE V (N=669)	TAXUS (N=333)	XIENCE V 4.0 mm Arm (N=69)	XIENCE V (N=223)	TAXUS (N=77)	XIENCE V (N=27)	VISION (N=29)
In Hospital							
TVF[1]	0.9% (6/669)	2.4% (8/330)	4.3% (3/69)	0.9% (2/223)	2.6% (2/77)	3.7% (1/27)	0.0% (0/28)
MACE[2]	0.9% (6/669)	2.4% (8/330)	4.3% (3/69)	0.9% (2/223)	2.6% (2/77)	3.7% (1/27)	0.0% (0/28)
All Death	0.0% (0/669)	0.0% (0/330)	0.0% (0/69)	0.0% (0/223)	0.0% (0/77)	0.0% (0/27)	0.0% (0/28)
Cardiac Death	0.0% (0/669)	0.0% (0/330)	0.0% (0/69)	0.0% (0/223)	0.0% (0/77)	0.0% (0/27)	0.0% (0/28)
Non-Cardiac Death	0.0% (0/669)	0.0% (0/330)	0.0% (0/69)	0.0% (0/223)	0.0% (0/77)	0.0% (0/27)	0.0% (0/28)
MI	0.7% (5/669)	2.4% (8/330)	4.3% (3/69)	0.9% (2/223)	2.6% (2/77)	0.0% (0/27)	0.0% (0/28)
QMI	0.0% (0/669)	0.0% (0/330)	0.0% (0/69)	0.0% (0/223)	0.0% (0/77)	0.0% (0/27)	0.0% (0/28)
NQMI	0.7% (5/669)	2.4% (8/330)	4.3% (3/69)	0.9% (2/223)	2.6% (2/77)	0.0% (0/27)	0.0% (0/28)
Cardiac Death or MI	0.7% (5/669)	2.4% (8/330)	4.3% (3/69)	0.9% (2/223)	2.6% (2/77)	0.0% (0/27)	0.0% (0/28)
Ischemia-Driven Revascularization	0.1% (1/669)	0.0% (0/330)	0.0% (0/69)	0.0% (0/223)	0.0% (0/77)	3.7% (1/27)	0.0% (0/28)
Ischemia-Driven TLR	0.1% (1/669)	0.0% (0/330)	0.0% (0/69)	0.0% (0/223)	0.0% (0/77)	3.7% (1/27)	0.0% (0/28)
Ischemia-Driven Non-TLR TVR	0.0% (0/669)	0.0% (0/330)	0.0% (0/69)	0.0% (0/223)	0.0% (0/77)	0.0% (0/27)	0.0% (0/28)
Stent Thrombosis[3] (Per Protocol)	0.3% (2/669)	0.0% (0/330)	1.4% (1/69)	0.0% (0/223)	0.0% (0/77)	0.0% (0/27)	0.0% (0/28)
9 Months[4]							
TVF[1]	7.6% (50/657)	9.7% (31/320)	5.9% (4/68)	4.5 (10/220)	6.5% (5/77)	7.7% (2/26)	21.4% (6/28)
MACE[2]	5.0% (33/657)	8.8% (28/320)	5.9% (4/68)	2.7% (6/220)	6.5% (5/77)	7.7% (2/26)	21.4% (6/28)
All Death	1.1% (7/658)	0.9% (3/321)	1.5% (1/68)	0.9% (2/222)	1.3% (1/77)	0.0% (0/26)	0.0% (0/28)
Cardiac Death	0.6% (4/658)	0.6% (2/321)	1.5% (1/68)	0.0% (0/222)	1.3% (1/77)	0.0% (0/26)	0.0% (0/28)

	SPIRIT III			SPIRIT II		SPIRIT FIRST	
	XIENCE V (N=669)	TAXUS (N=333)	XIENCE V 4.0 mm Arm (N=69)	XIENCE V (N=223)	TAXUS (N=77)	XIENCE V (N=27)	VISION (N=29)
Non-Cardiac Death	0.5% (3/658)	0.3% (1/321)	0.0% (0/68)	0.9% (2/222)	0.0% (0/77)	0.0% (0/26)	0.0% (0/28)
MI	2.3% (15/657)	3.1% (10/320)	4.4% (3/68)	0.9% (2/220)	3.9% (3/77)	3.8% (1/26)	0.0% (0/28)
QMI	0.2% (1/657)	0.0% (0/320)	0.0% (0/68)	0.0% (0/220)	0.0% (0/77)	3.8% (1/26)	0.0% (0/28)
NQMI	2.1% (14/657)	3.1% (10/320)	4.4% (3/68)	0.9% (2/220)	3.9% (3/77)	0.0% (0/26)	0.0% (0/28)
Cardiac Death or MI	2.9% (19/657)	3.8% (12/320)	5.9% (4/68)	0.9% (2/220)	3.9% (3/77)	3.8% (1/26)	0.0% (0/28)
Ischemia-Driven Revascularization	5.3% (35/657)	6.6% (21/320)	1.5% (1/68)	3.6% (8/220)	3.9% (3/77)	3.8% (1/26)	21.4% (6/28)
Ischemia-Driven TLR	2.7% (18/657)	5.0% (16/320)	1.5% (1/68)	1.8% (4/220)	3.9% (3/77)	3.8% (1/26)	21.4% (6/28)
Ischemia-Driven TVR, non TLR TVR	2.9% (19/657)	4.1% (13/320)	0.0% (0/68)	1.8% (4/220)	1.3% (1/77)	0.0% (0/26)	0.0% (0/28)
Stent Thrombosis[3]							
Protocol	0.6% (4/654)	0.0% (0/319)	1.5% (1/67)	0.5% (1/220)	1.3% (1/77)	0.0% (0/26)	0.0% (0/28)
1 Year[5]							
TVF[1]	8.6% (56/653)	11.3% (36/320)	5.9% (4/68)	4.5% (10/220)	9.1% (7/77)	15.4% (4/26)	21.4% (6/28)
MACE[2]	6.0% (39/653)	10.3% (33/320)	5.9% (4/68)	2.7% (6/220)	9.1% (7/77)	15.4% (4/26)	21.4% (6/28)
All Death	1.2% (8/655)	1.2% (4/321)	1.5% (1/68)	0.9% (2/222)	1.3% (1/77)	0.0% (0/26)	0.0% (0/28)
Cardiac Death	0.8% (5/655)	0.9% (3/321)	1.5% (1/68)	0.0% (0/222)	1.3% (1/77)	0.0% (0/26)	0.0% (0/28)
Non Cardiac Death	0.5% (3/655)	0.3% (1/321)	0.0% (0/68)	0.9% (2/222)	0.0% (0/77)	0.0% (0/26)	0.0% (0/28)
MI	2.8% (18/653)	4.1% (13/320)	4.4% (3/68)	0.9% (2/220)	3.9% (3/77)	7.7% (2/26)	0.0% (0/28)
QMI	0.3% (2/653)	0.3% (1/320)	0.0% (0/68)	0.0% (0/220)	0.0% (0/77)	3.8% (1/26)	0.0% (0/28)
NQMI	2.5% (16/653)	3.8% (12/320)	4.4% (3/68)	0.9% (2/220)	3.9% (3/77)	3.8% (1/26)	0.0% (0/28)
Cardiac Death or MI	3.4% (22/653)	4.7% (15/320)	5.9% (4/68)	0.9% (2/220)	3.9% (3/77)	7.7% (2/26)	0.0% (0/28)
Ischemia-Driven Revascularization	6.1% (40/653)	7.5% (24/320)	1.5% (1/68)	3.6% (8/220)	6.5% (5/77)	7.7% (2/26)	21.4% (6/28)
Ischemia-Driven TLR	3.4% (22/653)	5.6% (18/320)	1.5% (1/68)	1.8% (4/220)	6.5% (5/77)	7.7% (2/26)	21.4% (6/28)
Ischemia-Driven non-TLR TVR	3.1% (20/653)	4.4% (14/320)	0.0% (0/68)	1.8% (4/220)	1.3% (1/77)	0.0% (0/26)	0.0% (0/28)
Stent Thrombosis[3]							
Per Protocol	0.8% (5/647)	0.6% (2/317)	1.5% (1/67)	0.5% (1/220)	1.3% (1/77)	0.0% (0/26)	0.0% (0/28)
ARC (Definite+Probable)	1.1% (7/648)	0.6% (2/317)	0.0% (0/67)	0.0% (0/220)	1.3% (1/77)	0.0% (0/26)	0.0% (0/28)

	SPIRIT III			SPIRIT II		SPIRIT FIRST	
	XIENCE V (N=669)	TAXUS (N=333)	XIENCE V 4.0 mm Arm (N=69)	XIENCE V (N=223)	TAXUS (N=77)	XIENCE V (N=27)	VISION (N=29)

Notes:

- In-hospital is defined as hospitalization less than or equal to 7 days post-index procedure.
- All counts presented in this table are subject counts. Subjects are counted only once for each event for each time period.
- This table includes revascularizations on any target vessel(s)/lesion(s) for subjects with two target vessels / lesions treated.
- One subject in the SPIRIT III, TAXUS arm did not provide written informed consent and was inadvertently randomized into the study. Data from this subject is excluded from all data analyses.
- SPIRIT II and III based on Intent to Treat Population (all subjects randomized, regardless of the treatment they actually received).
- SPIRIT FIRST based on per-treatment evaluable population [a subset of subjects in the full analysis set, who had no bailout and no major protocol deviations other than those relating to treatment arm (randomized versus actually received)].
- Revascularization includes TLR and Non-TLR TVR.
- Q wave MI for all SPIRIT Trials is defined as the development of new pathological Q wave on the ECG.
- Non Q wave MI for SPIRIT III is defined as the elevation of CK levels to greater than or equal to 2 times the upper limit of normal with elevated CKMB in the absence of new pathological Q waves.
- Non Q wave MI for SPIRIT II is defined as a typical rise and fall of CKMB with at least one of the following: Ischemia symptoms, ECG changes indicative of ischemia (ST segment elevation or depression), or coronary artery intervention.
    - If non procedural/spontaneous MI, CKMB is greater than or equal to 2 times upper limit of normal
    - If post PCI, CKMB is greater than or equal to 3 times upper limit of normal
    - If post CABG, CKMB is greater than or equal to 5 times upper limit of normal
- Non Q wave MI for SPIRIT FIRST is defined (WHO definition) as the elevation of post procedure CK levels to greater than or equal to 2 times the upper normal limit with elevated CKMB in the absence of new pathological Q waves.
- Non Q wave MI for SPIRIT FIRST is defined (ESC/ACC definition) as for non procedural, CKMB elevation greater than or equal to 2 times the upper normal limit, for post PCI, CKMB elevation greater than or equal to three times the upper normal limit, and for post CBAG, CKMB elevation greater than or equal to five times the upper normal limit.

[1] TVF includes cardiac death, MI, ischemia-driven TLR and TVR, non-target lesion.
[2] MACE includes cardiac death, MI and ischemia-driven TLR.
[3] See Section 8.2 – Stent Thrombosis Definitions.
[4] SPIRIT III and SPIRIT FIRST includes 14 day window. SPIRIT III includes 9 month events identified at the 1 year follow-up.
[5] SPIRIT III and SPIRIT FIRST includes 28 day window.

Table 8.1-2: SPIRIT III, II and FIRST: Principal Adverse Events from Latest Follow-up

	SPIRIT III 1 Year[4]			SPIRIT II 2 Year[4]		SPIRIT FIRST 3 Year[4]	
	XIENCE V (N=669)	TAXUS (N=333)	XIENCE V 4.0 mm Arm (N=69)	XIENCE V (N=223)	TAXUS (N=77)	XIENCE V (N=27)	VISION (N=29)
TVF[1]	8.6% (56/653)	11.3% (36/320)	5.9% (4/68)	10.0% (21/211)	12.3% (9/73)	15.4% (4/26)	32.1% (9/28)
MACE[2]	6.0% (39/653)	10.3% (33/320)	5.9% (4/68)	6.6% (14/211)	11.0% (8/73)	15.4% (4/26)	25.0% (7/28)
All Death	1.2% (8/655)	1.2% (4/321)	1.5% (1/68)	3.7% (8/218)	6.5% (5/77)	0.0% (0/26)	0.0% (0/28)
Cardiac Death	0.8% (5/655)	0.9% (3/321)	1.5% (1/68)	0.5% (1/218)	1.3% (1/77)	0.0% (0/26)	0.0% (0/28)
Non-Cardiac Death	0.5% (3/655)	0.3% (1/321)	0.0% (0/68)	3.2% (7/218)	5.2% (4/77)	0.0% (0/26)	0.0% (0/28)
MI	2.8% (18/653)	4.1% (13/320)	4.4% (3/68)	2.8% (6/211)	5.5% (4/73)	7.7% (2/26)	0.0% (0/28)
QMI	0.3% (2/653)	0.3% (1/320)	0.0% (0/68)	0.0% (0/211)	0.0% (0/73)	3.8% (1/26)	0.0% (0/28)
NQMI	2.5% (16/653)	3.8% (12/320)	4.4% (3/68)	2.8% (6/211)	5.5% (4/73)	3.8% (1/26)	0.0% (0/28)
Cardiac Death or MI	3.4% (22/653)	4.7% (15/320)	5.9% (4/68)	3.3% (7/211)	5.5% (4/73)	7.7% (2/26)	0.0% (0/28)
Ischemia-Driven Revascularization	6.1% (40/653)	7.5% (24/320)	1.5% (1/68)	7.1% (15/211)	9.6% (7/73)	7.7% (2/26)	32.1% (9/28)
Ischemia-Driven TLR	3.4% (22/653)	5.6% (18/320)	1.5% (1/68)	3.8% (8/211)	6.8% (5/73)	7.7% (2/26)	25.0% (7/28)
Ischemia-Driven non-TLR TVR	3.1% (20/653)	4.4% (14/320)	0.0% (0/68)	3.8% (8/211)	4.1% (3/73)	0.0% (0/26)	10.7% (3/28)
Stent Thrombosis[3]							
Per Protocol	0.8% (5/647)	0.6% (2/317)	1.5% (1/67)	1.9% (4/211)	1.4% (1/73)	0.0% (0/26)	0.0% (0/28)
ARC (Definite+Probable)	1.1% (7/648)	0.6% (2/317)	0.0% (0/67)	0.9% (2/211)	1.4% (1/73)	0.0% (0/26)	0.0% (0/28)

Notes:
- In-hospital is defined as hospitalization less than or equal to 7 days post-index procedure.
- All counts presented in this table are subject counts. Subjects are counted only once for each event for each time period.
- This table includes revascularizations on any target vessel(s)/lesion(s) for subjects with two target vessels / lesions treated.
- One subject in the SPIRIT III, TAXUS arm did not provide written informed consent and was inadvertently randomized into the study. Data from this subject is excluded from all data analyses.
- SPIRIT II and III based on Intent to Treat Population (all subjects randomized, regardless of the treatment they actually received).
- SPIRIT FIRST based on per-treatment evaluable population [a subset of subjects in the full analysis set, who had no bailout and no major protocol deviations other than those relating to treatment arm (randomized versus actually received)].
- Revascularization includes TLR and Non-TLR TVR.

[1] TVF includes cardiac death, MI, ischemia-driven TLR and TVR, non-target lesion.
[2] MACE includes cardiac death, MI and ischemia-driven TLR.
[3] See Section 8.2 – Stent Thrombosis Definitions.
[4] SPIRIT III, SPIRIT II and SPIRIT FIRST includes 28 day window.

8.2 Stent Thrombosis Definitions

Protocol defined stent thrombosis (ST) was categorized as acute (< 1 day), subacute (1 - 30 days) and late (> 30 days) and was defined as any of the following[5]:

- Clinical presentation of acute coronary syndrome with angiographic evidence of stent thrombosis (angiographic appearance of thrombus within or adjacent to a previously treated target lesion)
- In the absence of angiography, any unexplained death, or acute MI (ST segment elevation or new Q-wave)[6] in the distribution of the target lesion within 30 days

All stent thrombosis events were also classified using the ST definitions proposed by the Academic Research Consortium (ARC)[7]. This was performed by an independent event committee blinded to the treatment group of the individual subject. The committee categorized each incident of ST by timing and level of probability (definite, probable, possible), and relation to the original index procedure (primary, secondary after revascularization). These categories are defined as follows:

Timing:

- Early ST: 0 to 30 days post stent implantation
- Late ST: 31 days to 1 year post stent implantation
- Very late ST: > 1 year post stent implantation

Level of probability:

- Definite ST - considered to have occurred by either angiographic or pathologic confirmation
- Probable ST - considered to have occurred after intracoronary stenting in the following cases:
    1. Any unexplained death within the first 30 days.
    2. Irrespective of the time after the index procedure, any MI which is related to documented acute ischemia in the territory of the implanted stent without angiographic confirmation of ST and in the absence of any other obvious cause.
- Possible ST - considered to have occurred with any unexplained death following 30 days after the intracoronary stenting until the end of trial follow-up[8]

8.3 Potential Adverse Events

Adverse events (in alphabetical order) which may be associated with percutaneous coronary and treatment procedures including coronary stent use in native coronary arteries include, but are not limited to:

- Abrupt closure
- Access site pain, hematoma, or hemorrhage
- Acute myocardial infarction

[5] For SPIRIT FIRST Stent Thrombosis is defined as total occlusion by angiography at the stent site with abrupt onset of symptoms, elevated biochemical markers, and ECG changes consistent with MI.

[6] Non-specific ST/T changes, and cardiac enzyme elevations do not suffice.

[7] Cutlip DE, Windecker S, Mehran R, et al. Clinical end points in coronary stent trials: a case for standardized definitions. *Circ* 2007;115:2344-51.

[8] All data within this Instructions for Use is presented as definite + probable only.

- Allergic reaction or hypersensitivity to contrast agent or cobalt, chromium, nickel, tungsten, acrylic and fluoropolymers; and drug reactions to antiplatelet drugs or contrast agent
- Aneurysm
- Arterial perforation and injury to the coronary artery
- Arterial rupture
- Arteriovenous fistula
- Arrhythmias, atrial and ventricular
- Bleeding complications, which may require transfusion
- Cardiac tamponade
- Coronary artery spasm
- Coronary or stent embolism
- Coronary or stent thrombosis
- Death
- Dissection of the coronary artery
- Distal emboli (air, tissue or thrombotic)
- Emergent or non-emergent coronary artery bypass graft surgery
- Fever
- Hypotension and/or hypertension
- Infection and pain at insertion site
- Injury to the coronary artery
- Ischemia (myocardial)
- Myocardial infarction (MI)
- Nausea and vomiting
- Palpitations
- Peripheral ischemia (due to vascular injury)
- Pseudoaneurysm
- Renal failure
- Restenosis of the stented segment of the artery
- Shock/pulmonary edema
- Stroke/cerebrovascular accident (CVA)
- Total occlusion of coronary artery
- Unstable or stable angina pectoris
- Vascular complications including at the entry site which may require vessel repair
- Vessel dissection

Adverse events associated with daily oral administration of everolimus to organ transplant patients include but are not limited to:

- Abdominal pain
- Acne
- Anemia
- Coagulopathy
- Diarrhea
- Edema
- Hemolysis
- Hypercholesterolemia
- Hyperlipidemia

- Hypertension
- Hypertriglyceridemia
- Hypogonadism male
- Infections: wound infection, urinary tract infection, pneumonia, pyelonephritis, sepsis and other viral, bacterial and fungal infections
- Leukopenia
- Liver function test abnormality
- Lymphocele
- Myalgia
- Nausea
- Pain
- Rash
- Renal tubular necrosis
- Surgical wound complication
- Thrombocytopenia
- Venous thromboembolism
- Vomiting

There may be other potential adverse events that are unforeseen at this time.

9.0 XIENCE V SPIRIT FAMILY OF CLINICAL TRIALS

9.1 SPIRIT III Pivotal Clinical Trial

SPIRIT III, a pivotal clinical trial, was designed to demonstrate the non-inferiority of the XIENCE V stent to the TAXUS EXPRESS^{2}™ Paclitaxel Eluting Coronary Stent System (TAXUS stent) and was conducted in the United States (US) and Japan. The SPIRIT III clinical trial consists of a US randomized clinical trial (RCT), a non-randomized 4.0 mm diameter stent arm in the US, and a non-randomized arm in Japan, which included a pharmacokinetic substudy. Enrollment is complete in the RCT and the Japan arm.

The SPIRIT III clinical trial included a pharmacokinetic substudy in a subject subset derived from the RCT[9] and Japan non-randomized arm (see Section 6.2 Pharmacokinetics of the XIENCE V Everolimus Eluting Coronary Stent). Eleven sites in the US and 9 sites in Japan participated in this substudy and have enrolled 34 subjects (17 subjects in the US and 17 subjects in Japan). Venous blood was drawn at regular intervals for pharmacokinetics analysis of total blood everolimus level at pre-determined sites.

9.1.1 SPIRIT III Randomized Clinical Trial (RCT)

Primary Objective: The objective of the SPIRIT III RCT was to demonstrate the non-inferiority in in-segment late loss at 240 days and target vessel failure at 270 days of the XIENCE V stent compared to the TAXUS stent in the treatment of up to two *de novo* lesions ≤ 28 mm in length in native coronary arteries with a reference vessel diameter (RVD) ≥ 2.5 mm to ≤ 3.75 mm. If non-inferiority of in-segment late loss was demonstrated, it was pre-specified that testing for superiority could be conducted.

[9] Includes one subject from the 4.0 mm non-randomized arm

Design: The SPIRIT III RCT was a prospective, 2:1 (XIENCE V:TAXUS) randomized, active-controlled, single-blinded, parallel, multi-center non-inferiority evaluation of the XIENCE V stent compared to the TAXUS stent in the treatment of up to two *de novo* lesions ≤ 28 mm in length in native coronary arteries with RVD ≥ 2.5 mm to ≤ 3.75 mm. Given the available XIENCE V stent lengths of 8, 18 and 28 mm for this trial, in the XIENCE V arm, treatment of a target lesion > 22 mm and ≤ 28 mm in length was accomplished by planned overlap of either two 18 mm stents or a 28 mm and an 8 mm stent. In the TAXUS arm, overlap was only permitted for bailout or to ensure adequate lesion coverage. The RCT was designed to enroll 1,002 subjects at up to 80 sites in the United States.

All subjects had clinical follow-up at 30, 180, and 270 days and annually from 1 to 5 years. A pre-specified subgroup of 564 subjects had angiographic follow-up at 240 days. Of these 564, 240 subjects had IVUS at baseline and 240 days. Subjects that received a bailout stent also had IVUS at baseline and angiographic and IVUS follow-up at 240 days.

Following the index procedure, all subjects were to be maintained on clopidogrel bisulfate daily for a minimum of 6 months and aspirin daily to be taken throughout the length of the trial (5 years).

Demographics: The mean age was 63.2 years for the XIENCE V arm and 62.8 for the TAXUS arm. The XIENCE V had 70.1% (469/669) males and the TAXUS arm had 65.7% (218/332) males. The XIENCE V arm had 32.3% (215/666) of subjects with prior cardiac interventions and the TAXUS arm had 29.5% (98/332). The XIENCE V arm had 29.6% (198/669) of subjects with a history of diabetes and the TAXUS arm had 27.9% (92/330). The XIENCE V had 15.4% (103/669) of subjects with a lesion treated in two vessels and TAXUS had 15.4% (51/332). The XIENCE V arm had 8.1% (54/669) of subjects with planned stent overlap. The XIENCE V arm had 8.6% (57/666) of subjects with a history of prior CABG while the TAXUS arm had 3.6% (12/332) ($p = 0.0033$). The XIENCE V arm had 18.7% (123/657) of subjects with a history of unstable angina while the TAXUS arm had 25.1% (82/327) ($p=0.0243$). The remaining subject baseline clinical features were well-matched between the XIENCE V arm and the TAXUS arm.

Results: The results are presented in Table 9.1.1-1 (Primary endpoints), Table 9.1.1-2 (Clinical Results), Table 9.1.1-3 (Angiographic and IVUS Results), Figure 9.1.1-1 (TVF Free Survival) and Table 9.1.1-4 (ARC-Defined Stent Thrombosis). These analyses are based on the intent to treat population.

The co-primary endpoint of in-segment late loss at 240 days was met with measurements of 0.14 ± 0.41 mm (301) for the XIENCE V arm and 0.28 ± 0.48 mm (134) for the TAXUS arm ($p < 0.0001$ for non-inferiority). In a prespecified analysis, the XIENCE V stent was shown to be superior to the TAXUS stent with respect to in-segment late loss at 240 days ($p = 0.0037$).

The co-primary endpoint of ischemia-driven TVF through 284 days was met with rates of 7.6% (50/657) for the XIENCE V arm and 9.7% (31/320) for the TAXUS arm ($p < 0.001$ for non-inferiority).

Table 9.1.1-1: SPIRIT III RCT Primary Endpoints Results

Measurements	XIENCE V (N=669) (M=376)	TAXUS (N=333) (M=188)	Difference [95% CI]	Non-Inferiority P-Value	Superiority P-Value
8 Month[1] Late Loss, In-segment (mm)	0.14 ± 0.41 (301)	0.28 ± 0.48 (134)	-0.14 [-0.23, -0.05][2]	<0.0001[3]	0.0037[4]
9 Month[5] Target Vessel Failure[6]	7.6% (50/657)	9.7% (31/320)	-2.08% [-5.90%, 1.75%][2]	<0.0001[7]	Not Pre-specified

Notes:

- N is the total number of subjects; M is the total number of analysis lesions.
- One in SPIRIT III TAXUS arm subject did not provide written informed consent and was inadvertently randomized into the study. Data from this subject is excluded from all data analyses.
- Analysis results include 9 month events identified at the 1 year follow-up.

[1] 8 month time frame includes follow-up window (240 + 28 days).
[2] By normal approximation.
[3] One-sided p-value by non-inferiority test using asymptotic test statistic with non-inferiority margin of 0.195 mm, to be compared at a 0.025 significance level.
[4] Two-sided p-value by superiority test using two-sample T-test, to be compared at a 0.05 significance level.
[5] 9 month time frame includes follow-up window (270 + 14 days).
[6] TVF is defined as hierarchical composite of cardiac death, MI, ischemic-driven TLR and ischemic-driven non-TLR TVR.
[7] One sided p-value by non-inferiority test using asymptotic test statistic with non-inferiority margin of 5.5%, to be compared at a 0.05 significance level.

Table 9.1.1-2: SPIRIT III RCT Clinical Results

	OUTCOMES AT 9 MONTHS			OUTCOMES AT 1 YEAR (latest available follow-up)		
	XIENCE V (N=669)	TAXUS (N=333)	Difference [95% CI][1]	XIENCE V (N=669)	TAXUS (N=333)	Difference [95% CI][1]
COMPOSITE EFFICACY & SAFETY						
TVF[2]	7.6% (50/657)	9.7% (31/320)	-2.08% [-5.90%, 1.75%]	8.6% (56/653)	11.3% (36/320)	-2.67% [-6.75%, 1.40%]
MACE[3]	5.0% (33/657)	8.8% (28/320)[7]	-3.73% [-7.24%, -0.21%]	6.0% (39/653)	10.3% (33/320)	-4.34% [-8.14%, -0.54%]
EFFICACY						
Ischemia-Driven TLR	2.7% (18/657)	5.0% (16/320)	-2.26% [-4.95%, 0.43%]	3.4% (22/653)	5.6% (18/320)	-2.26% [-5.13%, 0.62%]
TLR, CABG	0.2% (1/657)	0.0% (0/320)	0.15% [Assump. not met]	0.3% (2/653)	0.0% (0/320)	0.31% [Assump. not met]
TLR, PCI	2.6% (17/657)	5.0% (16/320)	-2.41% [-5.09%, 0.27%]	3.1% (20/653)	5.6% (18/320)	-2.56% [-5.41%, 0.29%]
Ischemia-Driven non-TLR TVR	2.9% (19/657)	4.1% (13/320)	-1.17% [-3.68%, 1.34%]	3.1% (20/653)	4.4% (14/320)	-1.31% [-3.91%, 1.29%]
non-TLR TVR, CABG	0.5% (3/657)	0.6% (2/320)	-0.17% [Assump. not met]	0.6% (4/653)	0.6% (2/320)	-0.01% [Assump. not met]
non-TLR TVR, PCI	2.4% (16/657)	3.4% (11/320)	-1.00% [-3.32%, 1.32%]	2.5% (16/653)	3.8% (12/320)	-1.30% [-3.70%, 1.10%]
SAFETY						
All Death	1.1% (7/658)	0.9% (3/321)	0.13% [Assump. not met]	1.2% (8/655)	1.2% (4/321)	-0.02% [Assump. not met]
Cardiac Death	0.6% (4/658)	0.6% (2/321)	-0.02% [Assump. not met]	0.8% (5/655)	0.9% (3/321)	-0.17% [Assump. not met]
Non-Cardiac Death	0.5% (3/658)	0.3% (1/321)	0.14% [Assump. not met]	0.5% (3/655)	0.3% (1/321)	0.15% [Assump. not met]
MI	2.3% (15/657)	3.1% (10/320)	-0.84% [-3.06%, 1.38%]	2.8% (18/653)	4.1% (13/320)	-1.31% [-3.81%, 1.20%]
QMI	0.2% (1/657)	0.0% (0/320)	0.15% [Assump. not met]	0.3% (2/653)	0.3% (1/320)	-0.01% [Assump. not met]
NQMI	2.1% (14/657)	3.1% (10/320)	-0.99% [-3.20%, 1.21%]	2.5% (16/653)	3.8% (12/320)	-1.30% [-3.70%, 1.10%]
Cardiac Death or MI	2.9% (19/657)	3.8% (12/320)	-0.86% [-3.30%, 1.59%]	3.4% (22/653)	4.7% (15/320)	-1.32% [-4.02%, 1.38%]
Stent Thrombosis – Protocol defined	0.6% (4/654)	0.0% (0/319)	0.61% [Assump. not met]	0.8% (5/647)	0.6% (2/317)	0.14% [Assump. not met]
Acute (< 1 day)	0.1% (1/669)	0.0% (0/330)	0.15% [Assump. not met]	0.1% (1/669)	0.0% (0/330)	0.15% [Assump. not met]
Subacute (1 – 30 days)	0.3% (2/667)	0.0% (0/330)	0.30% [Assump. not met]	0.3% (2/667)	0.0% (0/330)	0.30% [Assump. not met]
Late (> 30 days)	0.2% (1/653)	0.0% (0/319)	0.15% [Assump. not met]	0.3% (2/646)	0.6% (2/317)	-0.32% [Assump. not met]

Notes:

- One subject in SPIRIT III TAXUS arm did not provide written informed consent and was inadvertently randomized into the study. Data from this subject is excluded from all data analyses.
- 9 month and 1 year time frames include follow-up window (270 +14 days and 365 + 28 days) respectively.
- 9 months analysis results include 9 month events identified at the 1 year follow-up.
- Assump. not met means that assumption of normal approximation not met due to small sample size or frequency of events.

[1] Confidence Interval was calculated using the normal approximation, not adjusted for multiplicity and is meant for descriptive purposes only.
[2] TVF is defined as a hierarchical composite of cardiac death, MI, ischemic-driven TLR and ischemic-driven non-TLR TVR.
[3] MACE is defined as a hierarchical composite of cardiac death, MI, ischemic-driven TLR.

Table 9.1.1-3: SPIRIT III 8 Month Angiographic and IVUS Results

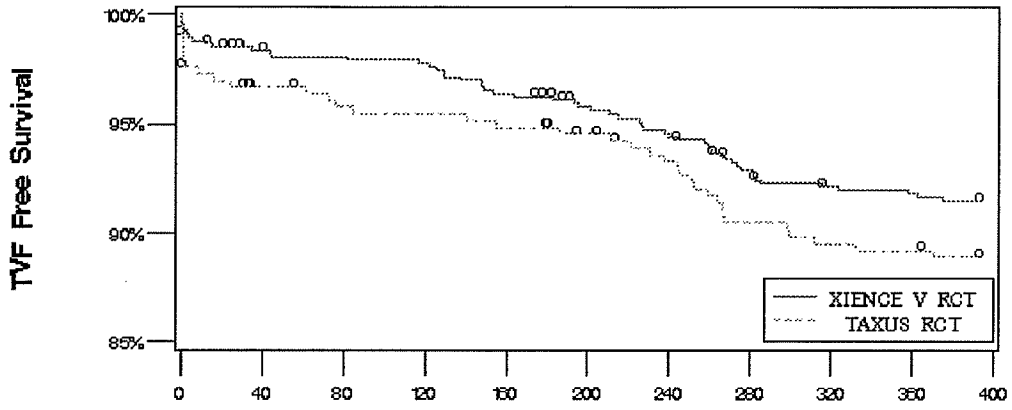
	XIENCE V (N=376) (M_{ANGIO}=427) (M_{IVUS}=181)	TAXUS (N=188) (M_{ANGIO}=220) (M_{IVUS}=93)	Difference [95% CI][1]
ANGIOGRAPHIC RESULTS			
In-Stent MLD			
Post-Procedure	2.71 ± 0.43 (425)	2.74 ± 0.40 (220)	-0.03 [-0.10, 0.04]
8 Months	2.56 ± 0.53 (343)	2.45 ± 0.65 (158)	0.11 [-0.01, 0.23]
In-Segment MLD			
Post-Procedure	2.35 ± 0.44 (426)	2.36 ± 0.45 (220)	-0.01 [-0.08, 0.06]
8 Months	2.22 ± 0.53 (344)	2.12 ± 0.60 (158)	0.10 [-0.01, 0.21]
In-Stent %DS			
Post-Procedure	0.32 ± 8.86 (424)	-0.78 ± 10.65 (220)	1.10 [-0.55, 2.74]
8 Months	5.92 ± 16.40 (343)	10.30 ± 21.43 (158)	-4.38 [-8.16, -0.60]
In-Segment %DS			
Post-Procedure	13.89 ± 8.04 (425)	13.92 ± 7.20 (220)	-0.03 [-1.26, 1.19]
8 Months	18.77 ± 14.43 (344)	22.82 ± 16.35 (158)	-4.05 [-7.03, -1.06]
Late Loss			
In-Stent	0.16 ± 0.41 (342)	0.30 ± 0.53 (158)	-0.15 [-0.24, -0.05]
In-Segment	0.14 ± 0.39 (343)	0.26 ± 0.46 (158)	-0.13 [-0.21, -0.04]
Binary Restenosis			
In-Stent	2.3% (8/343)	5.7% (9/158)	-3.36% [-7.32%, 0.59%]
In-Segment	4.7% (16/344)	8.9% (14/158)	-4.21% [-9.17%, 0.75%]
IVUS RESULTS			
Neointimal Volume (mm^3)	10.13 ± 11.46 (101)	20.87 ± 13.51 (41)	-10.74 [-20.92, -0.56]
% Volume Obstruction	6.91 ± 6.35 (98)	11.21 ± 9.86 (39)	-4.30 [-7.72, -0.88]
Incomplete Apposition			
Post Procedure	34.4% (31/90)	25.6% (11/43)	8.86% [-7.46%, 25.19%]
8 month	25.6% (23/90)	16.3% (7/43)	9.28% [-4.97%, 23.52%]
Persistent	24.4% (22/90)	14.0% (6/43)	10.49% [-3.15%, 24.13%]
Late Acquired	1.1% (1/90)	2.3% (1/43)	-1.21% [Assump. not met]

Notes:

- N is the total number of subjects; M_{ANGIO} is the total number of lesions in the protocol required angiographic cohort and M_{IVUS} is the total number of lesions in the protocol required IVUS cohort.
- One subject in SPIRIT III TAXUS arm did not provide written informed consent and was inadvertently randomized into the study. Data from this subject is excluded from all data analyses.
- 8 month time frame includes follow-up window (240 + 28 days).
- Assump. not met means that assumption of normal approximation not met due to small sample size or frequency of events.

[1] Confidence Interval was calculated using the normal approximation, not adjusted for multiplicity and is meant for descriptive purposes only.

Figure 9.1.1-1: SPIRIT III: Survival Free of Target Vessel Failure through 1 Year



TVF	Event Free	Event Rate	P-value[1]
XIENCE V	91.5%	8.5%	0.18
TAXUS	88.9%	11.1%	

Note:
– Time Frame includes follow-up window (365 + 28 days).
[1]P-value based on log rank and not adjusted for multiple comparisons

Table 9.1.1-4: SPIRIT III RCT ARC defined Definite+Probable Stent Thrombosis Through 1 Year

	XIENCE V (N=669)	TAXUS (N=333)	Difference [95% CI][1]
ARC Definite+Probable Stent Thrombosis (0 days – 1 year)	1.1% (7/648)	0.6% (2/317)	0.45% [Assump. not met]
Acute (< 1 day)	0.1% (1/669)	0.0% (0/330)	0.15% [Assump. not met]
Subacute (1 – 30 days)	0.4% (3/667)	0.0% (0/330)	0.45% [Assump. not met]
Late (> 30 days)	0.5% (3/647)	0.6% (2/317)	-0.17% [Assump. not met]

Notes:
- One subject in SPIRIT III TAXUS arm did not provide written informed consent and was inadvertently randomized into the study. Data from this subject is excluded from all data analyses.
- Time Frame includes follow-up window (365 + 28 days).
- Assump. not met means that assumption of normal approximation not met due to small sample size or frequency of events.

[1] Confidence Interval was calculated using the normal approximation, not adjusted for multiplicity and is meant for descriptive purposes only.

9.1.2 SPIRIT III US 4.0 mm Arm

Primary Objective: The objective of the SPIRIT III 4.0 mm arm was to demonstrate the non-inferiority in in-segment late loss at 240 days compared to the TAXUS arm of the SPIRIT III RCT.

Design: The SPIRIT III 4.0 mm study was a prospective, single-arm, multi-center clinical trial in the United States evaluating the 4.0 mm diameter XIENCE V stent. Sixty-nine (69) subjects were enrolled in the SPIRIT III 4.0 mm study arm.

All subjects had clinical follow-up at 30, 180, 240, and 270 days, and annually from 1 to 5 years. In addition, all subjects had angiographic follow-up at 240 days. IVUS was performed for subjects who received a bailout stent at baseline and 240 days.

Following the index procedure, all subjects were to be maintained on clopidogrel bisulfate daily for a minimum of 6 months and aspirin daily to be taken throughout the length of the trial (5 years).

Demographics: The mean age in the SPIRIT III 4.0 arm was 61.9 years with 72.5% (50/69) male, 21.7% (15/69) had prior cardiac interventions, and 30.4% (21/69) had a history of diabetes.

Results: The results are presented in Table 9.1.2-1 (Primary endpoints), Table 9.1.2-2 (Clinical Results), Table 9.1.2-3 (Angiographic Results), and Table 9.1.2-4 (ARC-Defined Stent Thrombosis). These analyses were performed on the intent to treat population.

The primary endpoint of in-segment late loss at 240 days was met with measurements of 0.17 ± 0.38 mm (49) for the XIENCE V 4.0 mm arm and 0.28 ± 0.48 mm (134) for the TAXUS arm from the SPIRIT III RCT ($p < 0.0001$ for non-inferiority).

Table 9.1.2-1: SPIRIT III 4.0 mm Primary Endpoints Results

Measurements	XIENCE V (M=69)	TAXUS (M=188)	Difference [95% CI]	Non-Inferiority P-Value
8 Month Late Loss, In-segment (mm)	0.17 ± 0.38 (49)	0.28 ± 0.48 (134)	-0.11 [-0.24, 0.03][1]	<0.0001[2]

Notes:
- M is the total number of analysis lesions.
- One subject in SPIRIT III TAXUS arm did not provide written informed consent and was inadvertently randomized into the study. Data from this subject is excluded from all data analyses.
- Time Frame includes follow-up window (240 + 28 days).

[1] By normal approximation.
[2] One-sided p-value by non-inferiority test using asymptotic test statistic with non-inferiority margin of 0.195 mm, to be compared at a 0.038 significance level.

Table 9.1.2-2: SPIRIT III 4.0 mm Clinical Results

	OUTCOMES AT 9 MONTHS XIENCE V (N=69)	OUTCOMES AT 1 YEAR (latest available follow-up) XIENCE V (N=69)
COMPOSITE EFFICACY & SAFETY		
TVF[1]	5.9% (4/68)	5.9% (4/68)
MACE[2]	5.9% (4/68)	5.9% (4/68)
EFFICACY		
Ischemia-Driven TLR	1.5% (1/68)	1.5% (1/68)
TLR, CABG	0.0% (0/68)	0.0% (0/68)
TLR, PCI	1.5% (1/68)	1.5% (1/68)
Ischemia-Driven non-TLR TVR	0.0% (0/68)	0.0% (0/68)
non-TLR TVR, CABG	0.0% (0/68)	0.0% (0/68)
non-TLR TVR, PCI	0.0% (0/68)	0.0% (0/68)
SAFETY		
All Death	1.5% (1/68)	1.5% (1/68)
Cardiac Death	1.5% (1/68)	1.5% (1/68)
Non-Cardiac Death	0.0% (0/68)	0.0% (0/68)
MI	4.4% (3/68)	4.4% (3/68)
QMI	0.0% (0/68)	0.0% (0/68)
NQMI	4.4% (3/68)	4.4% (3/68)
Cardiac Death or MI	5.9% (4/68)	5.9% (4/68)
Stent Thrombosis – Protocol defined	1.5% (1/67)	1.5% (1/67)
Acute (< 1 day)	1.4% (1/69)	1.4% (1/69)
Subacute (1 – 30 days)	0.0% (0/69)	0.0% (0/69)
Late (> 30 days)	0.0% (0/67)	0.0% (0/67)

Notes:
- 9 months and 1 year time frames include follow-up window (270 +14 days and 365 + 28 days) respectively. 9 month analysis includes 9 month events identified at the 1 year follow-up.

[1] TVF is defined as a hierarchical composite of cardiac death, MI, ischemic-driven TLR and ischemic-driven non-TLR TVR.
[2] MACE is defined as a hierarchical composite of cardiac death, MI, ischemic-driven TLR.

Table 9.1.2-3: SPIRIT III 4.0 mm 8 Month Angiographic Results

	XIENCE V (N=69) (M=69)
ANGIOGRAPHIC RESULTS	
In-Stent MLD	
Post-Procedure	3.46 ± 0.38 (69)
8 Months	3.36 ± 0.46 (49)
In-Segment MLD	
Post-Procedure	3.07 ± 0.43 (69)
8 Months	2.91 ± 0.51 (49)
In-Stent %DS	
Post-Procedure	2.12 ± 10.27 (69)
8 Months	4.78 ± 13.20 (49)
In-Segment %DS	
Post-Procedure	13.42 ± 8.08 (69)
8 Months	17.92 ± 10.83 (49)
Late Loss	
In-Stent	0.12 ± 0.34 (49)
In-Segment	0.17 ± 0.38 (49)
Binary Restenosis	
In-Stent	0.0% (0/49)
In-Segment	2.0% (1/49)

Notes:
- N is the total number of subjects; M is the total number of lesions at baseline.
- 8 month time frame includes follow-up window (240 + 28 days).

Table 9.1.2-4: SPIRIT III 4.0 mm ARC defined Definite+Probable Stent Thrombosis Through 1 Year

	XIENCE V (N=69)
ARC Definite+Probable Stent Thrombosis (0 days – 1 year)	0.0% (0/67)
Acute (< 1 day)	0.0% (0/69)
Subacute (1 – 30 days)	0.0% (0/69)
Late (> 30 days)	0.0% (0/67)

Notes:
- Time Frame includes follow-up window (365 + 28 days).

9.2 SPIRIT II Supportive Clinical Trial

Primary Objective: The objective of the SPIRIT II clinical study was to demonstrate the non-inferiority in in-stent late loss at 180 days of the XIENCE V stent to the TAXUS stent in subjects with a maximum of two *de novo* native coronary artery lesions, each in a different epicardial vessel. The SPIRIT II clinical study arm allowed the treatment of *de novo* lesions ≤ 28 mm in length in coronary arteries with a reference vessel diameter (RVD) ≥ 2.5 mm to ≤ 4.25 mm. If non-inferiority of in-stent late loss was demonstrated, it was pre-specified that testing for superiority could be conducted. SPIRIT II was performed outside of the U.S.

Design: The SPIRIT II clinical study was a prospective, active-control, 3:1 (XIENCE V:TAXUS) randomized, single-blind, multi-center non-inferiority evaluation of the XIENCE V stent compared to the TAXUS stent in the treatment of up to two *de novo* lesions ≤ 28 mm in length in native coronary arteries with RVD ≥ 2.5 mm to ≤ 4.25 mm. Given the available Xience V stent lengths of 8, 18 and 28 mm for this trial, in the Xience V arm, treatment of a target lesion > 22 mm and ≤ 28 mm in length was accomplished by planned overlap of either two 18 mm stents or a 28 mm and an 8 mm stent. In the TAXUS arm, overlap was only permitted for bailout or to ensure adequate lesion coverage.

Three hundred (300) subjects were enrolled in the study at 28 international sites in Europe, India and New Zealand.

All subjects had clinical follow-up at 30, 180, and 270 days, and annually from 1 to 5 years. All subjects had angiographic follow-up at 180 days with planned additional angiographic and IVUS follow-up at 2 years in a pre-specified subgroup of 152 consecutively enrolled subjects at selected sites.

Following the index procedure, all subjects were to be maintained on clopidogrel bisulfate daily for a minimum of 6 months and aspirin daily to be taken throughout the length of the trial (5 years).

A subgroup of 39 subjects were enrolled in a pharmacokinetic (PK) substudy. Venous blood was drawn at regular intervals for PK analysis of total blood everolimus level at 7 pre-determined sites.

Demographics: The mean age was 62.0 years for the XIENCE V arm and 61.9 years for the TAXUS arm. The XIENCE V had 70.9% (158/223) males and the TAXUS arm had 79.2% (61/77) males. The XIENCE V arm had 23.3% (52/223) of subjects with prior cardiac interventions and the TAXUS arm had 22.1% (17/77). The XIENCE V arm had 22.9% (51/223) of subjects with a history of diabetes and the TAXUS arm had 23.7% (18/76). The XIENCE V had 16.6% (37/223) of subjects with a lesion treated in two vessels and TAXUS had 18.2% (14/77). The XIENCE V arm had 10.8% (24/223) of subjects with planned stent overlap. The XIENCE V arm had 18.4% (40/217) of subjects with a history of an MI within two months while the TAXUS arm had 7.8% (6/77) (p=0.0284). The remaining subject baseline clinical features were well-matched between the XIENCE V arm and the TAXUS arm.

Results: The results are presented in Table 9.2-1 (Primary endpoint), Table 9.2-2 (Clinical Results), Table 9.2-3 (Angiographic and IVUS Results), and Table 9.2-4 (ARC-Defined Stent Thrombosis). These analyses were based on the intent to treat population.

The primary endpoint of in-stent late loss at 180 days was met with measurements of 0.11 ± 0.27 mm (201) for the XIENCE V arm and 0.36 ± 0.39 mm (73) for the TAXUS arm ($p < 0.0001$ for non-inferiority). In a prespecified analysis, the XIENCE V stent was shown to be superior to the TAXUS stent with respect to in-stent late loss at 180 days ($p < 0.0001$).

Table 9.2-1: SPIRIT II Primary Endpoint Result

Measurements	XIENCE V (N=223) (M=201)	TAXUS (N=77) (M=73)	Difference [95% CI]	Non-Inferiority P-Value	Superiority P-Value
180 Day Late Loss, In-stent (mm)	0.11 ± 0.27 (201)	0.36 ± 0.39 (73)	-0.24 [-0.34, -0.15][1]	<0.0001[2]	<0.0001[3]

Notes:
– N is the number of subjects and M is the total number of analysis lesions.
[1]By normal approximation.
[2]One-sided p-value by non-inferiority test using asymptotic test statistic with non-inferiority margin of 0.16 mm, to be compared at a 0.0448 significance level.
[3]P-value from two-sided t-test.

Table 9.2-2: SPIRIT II Clinical Results

	OUTCOMES AT 6 MONTHS			OUTCOMES AT 2 YEARS (latest available follow-up)		
	XIENCE V (N=223)	TAXUS (N=77)	Difference [95% CI][1]	XIENCE V (N=223)	TAXUS (N=77)	Difference [95% CI][1]
COMPOSITE EFFICACY & SAFETY						
TVF[2]	3.6% (8/222)	6.5% (5/77)	-2.89% [-8.92%, 3.14%]	10.0% (21/211)	12.3% (9/73)	-2.38% [-10.93%, 6.18%]
MACE[3]	2.7% (6/222)	6.5% (5/77)	-3.79% [-9.69%, 2.11%]	6.6% (14/211)	11.0% (8/73)	-4.32% [-12.24%, 3.59%]
EFFICACY						
Ischemia-Driven TLR	1.8% (4/222)	3.9% (3/77)	-2.09% [Assump. not fulfilled]	3.8% (8/211)	6.8% (5/73)	-3.06% [-9.40%, 3.28%]
TLR, CABG	0.0% (0/222)	0.0% (0/77)	0.00% [Assump. not fulfilled]	0.0% (0/211)	0.0% (0/73)	0.00% [Assump. not met]
TLR, PCI	1.8% (4/222)	3.9% (3/77)	-2.09% [Assump. not fulfilled]	3.8% (8/211)	6.8% (5/73)	-3.06% [-9.40%, 3.28%]
Ischemia-Driven non-TLR TVR	0.9% (2/222)	1.3% (1/77)	-0.40% [Assump. not fulfilled]	3.8% (8/211)	4.1% (3/73)	-0.32% [Assump. not met]
non-TLR TVR, CABG	0.0% (0/222)	0.0% (0/77)	0.00% [Assump. not fulfilled]	0.5% (1/211)	0.0% (0/73)	0.47% [Assump. not met]
non-TLR TVR, PCI	0.9% (2/222)	1.3% (1/77)	-0.40% [Assump. not fulfilled]	3.3% (7/211)	4.1% (3/73)	-0.79% [Assump. not met]
SAFETY						
All Death	0.0% (0/222)	1.3% (1/77)	-1.30% [Assump. not fulfilled]	3.7% (8/218)	6.5% (5/77)	-2.82% [-8.87%, 3.22]
Cardiac Death	0.0% (0/222)	1.3% (1/77)	-1.30% [Assump. not fulfilled]	0.5% (1/218)	1.3% (1/77)	-0.84% [Assump. not met]
Non-Cardiac Death	0.0% (0/222)	1.3% (1/77)	-1.30% [Assump. not fulfilled]	3.2% (7/218)	5.2% (4/77)	-1.98% [Assump. not met]
MI	0.9% (2/222)	3.9% (3/77)	-3.00% [Assump. not fulfilled]	2.8% (6/211)	5.5% (4/73)	-2.64% [Assump. not met]
QMI	0.0% (0/222)	0.0% (0/77)	0.00% [Assump. not fulfilled]	0.0% (0/211)	0.0% (0/73)	0.00% [Assump. not met]
NQMI	0.9% (2/222)	3.9% (3/77)	-3.00% [Assump. not fulfilled]	2.8% (6/211)	5.5% (4/73)	-2.64% [Assump. not met]
Cardiac Death or MI	0.9% (2/222)	3.9% (3/77)	-3.00% [Assump. not fulfilled]	3.3% (7/211)	5.5% (4/73)	-2.16% [Assump. not met]
Stent Thrombosis – Protocol defined	0.5% (1/222)	1.3% (1/77)	-0.85% [Assump. not fulfilled]	1.9% (4/211)	1.4% (1/73)	0.53% [Assump. not met]
Acute (< 1 day)	0.0% (0/223)	0.0% (0/77)	0.00% [Assump. not fulfilled]	0.0% (0/223)	0.0% (0/77)	0.00% [Assump. not met]
Subacute (1 – 30 days)	0.0% (0/223)	0.0% (0/77)	0.00% [Assump. not fulfilled]	0.0% (0/223)	0.0% (0/77)	0.00% [Assump. not met]
Late (> 30 days)	0.5% (1/222)	1.3% (1/77)	-0.85% [Assump. not fulfilled]	1.9% (4/211)	1.4% (1/73)	0.53% [Assump. not met]

Notes:

- 6 months and 2 year time frames include follow-up window (180 +14 days and 730 + 28 days).
- Assump. not met means that assumption of normal approximation not met due to small sample size or frequency of events.

[1] Confidence Interval was calculated using the normal approximation, not adjusted for multiplicity and is meant for descriptive purposes only.
[2] TVF is defined as a hierarchical composite of cardiac death, MI, ischemic-driven TLR and ischemic-driven non-TLR TVR.
[3] MACE is defined as a hierarchical composite of cardiac death, MI, ischemic-driven TLR.

Table 9.2-3: SPIRIT II 180-Day Angiographic and IVUS Results

	XIENCE V (N=223) (M=260)	TAXUS (N=77) (M=91)	Difference [95% CI][1]
ANGIOGRAPHIC RESULTS			
In-Stent MLD			
Post-Procedure	2.49 ± 0.40 (260)	2.62 ± 0.45 (91)	-0.13 [-0.24, -0.03]
6 Months	2.38 ± 0.50 (237)	2.27 ± 0.54 (86)	0.10 [-0.03, 0.23]
In-Segment MLD			
Post-Procedure	2.15 ± 0.44 (260)	2.22 ± 0.53 (91)	-0.07 [-0.19, 0.05]
6 Months	2.10 ± 0.51 (237)	2.08 ± 0.54 (86)	0.02 [-0.11, 0.15]
In-Stent %DS			
Post-Procedure	13.01 ± 6.02 (260)	12.66 ± 5.53 (91)	0.35 [-1.01, 1.71]
6 Months	15.70 ± 9.88 (237)	20.89 ± 11.59 (86)	-5.18 [-7.96, -2.41]
In-Segment %DS			
Post-Procedure	22.51 ± 8.98 (260)	23.36 ± 11.20 (91)	-0.86 [-3.43, 1.72]
6 Months	23.61 ± 11.65 (237)	27.05 ± 12.68 (86)	-3.44 [-6.53, -0.35]
Late Loss			
In-Stent	0.12 ± 0.29 (237)	0.37 ± 0.38 (86)	-0.25 [-0.34, -0.16]
In-Segment	0.07 ± 0.33 (237)	0.15 ± 0.38 (86)	-0.08 [-0.17, 0.01]
Binary Restenosis			
In-Stent	1.3% (3/237)	3.5% (3/86)	-2.22% [Assump. not met]
In-Segment	3.4% (8/237)	5.8% (5/86)	-2.44% [-7.89%, 3.02%]
IVUS RESULTS			
Neointimal Volume (mm^3)	3.83 ± 6.55 (99)	14.42 ± 16.03 (40)	-10.60 [-15.87, -5.32]
% Volume Obstruction	2.51 ± 4.68 (99)	7.36 ± 7.05 (40)	-4.85 [-7.27, -2.42]
Incomplete Apposition			
Post Procedure	6.5% (7/108)	5.6% (2/36)	0.93% [Assump. not met]
6 month	2.9% (3/103)	0.0% (0/39)	2.91% [Assump. not met]
Persistent	2.5% (3/120)	0.0% (0/42)	2.50% [Assump. not met]
Late Acquired	0.0% (0/104)	0.0% (0/39)	0.00% [Assump. not met]

Notes:
- N is the total number of subjects; M is the total number of lesions.
- Assump. not met means that assumption of normal approximation not met due to small sample size or frequency of events.

[1] Confidence Interval was calculated using the normal approximation, not adjusted for multiplicity and is meant for descriptive purposes only.

Table 9.2-4: SPIRIT II ARC defined Definite+Probable Stent Thrombosis Through 2 Years

	XIENCE V (N=223)	TAXUS (N=77)	Difference [95% CI][1]
ARC Definite+Probable Stent Thrombosis (0 days – 2 years)	0.9% (2/211)	1.4% (1/73)	-0.42% [Assump. not met]
Acute (< 1 day)	0.0% (0/223)	0.0% (0/77)	0.00% [Assump. not met]
Subacute (1 – 30 days)	0.0% (0/223)	1.3% (1/77)	-1.30% [Assump. not met]
Late (31 days – 1 year)	0.0% (0/220)	1.3% (1/77)	-1.30% [Assump. not met]
Very Late (1 – 2 years)	0.9% (2/211)	0.0% (0/72)	0.95% [Assump. not met]

Note:
- Assump. not met means that assumption of normal approximation not met due to small sample size or frequency of events.

[1] Confidence Interval was calculated using the normal approximation, not adjusted for multiplicity and is meant for descriptive purposes only.

9.3 SPIRIT FIRST Randomized Clinical Trial

Objective: The objective of the SPIRIT FIRST randomized clinical trial was to assess the feasibility and performance of the XIENCE V stent (called VISION-E within the SPIRIT FIRST study) in the treatment of subjects with a single *de novo* native coronary artery lesion with reference vessel diameter (RVD) of 3.0 mm and lesion length ≤ 12 mm. This study compared the XIENCE V stent to a matched uncoated metallic stent control (MULTI-LINK VISION).

Design: SPIRIT FIRST was a single-blind multi-center randomized controlled trial to assess the safety and performance of everolimus eluting from a durable polymer on a cobalt chromium stent (XIENCE V stent). Sixty (60) subjects were enrolled in the study.

All subjects had clinical follow-up at 30, 180, and 270 days, and annually from 1 to 5 years. All subjects had angiography and IVUS at baseline and at 180 days and 1 year follow-up.

Following the index procedure, all subjects were to be maintained on clopidogrel bisulfate daily for a minimum of 3 months and aspirin daily to be taken throughout the length of the trial (1 year).

Demographics: The mean age was 64.2 years for the XIENCE V arm and 61.4 years for the VISION arm. The XIENCE V had 70.4% (19/27) males and the VISION arm had 75.9% (22/29) males. The XIENCE V arm had 18.5% (5/27) subjects with prior cardiac interventions and the VISION arm had to 6.9% (2/29). The XIENCE V arm had 11.1% (3/27) subjects with a history of diabetes and the VISION arm had 10.3% (3/29). XIENCE V arm had 70.4% (19/27) of subjects with hypertension requiring medication while the VISION arm had 41.4% (12/29) (p=0.035). The remaining subject baseline clinical features were also well-matched between the XIENCE V arm and the VISION arm.

Results: The results are presented in Table 9.3-1 (Primary endpoint), Table 9.3-2 (Clinical Results), Table 9.3-3 (Angiographic and IVUS Results), and Table 9.3-4 (ARC-Defined Stent Thrombosis). These analyses were based on the per protocol evaluable population.

The primary superiority endpoint of in-stent late loss at 180 days was met with measurements of 0.10 ± 0.23 mm (23) for the XIENCE V arm and 0.85 ± 0.36 mm (27) for the MULTI-LINK VISION arm ($p < 0.0001$).

Table 9.3-1: SPIRIT FIRST Primary Endpoint Result

Measurements	XIENCE V (N = 27)	VISION (N = 29)	Difference [95% CI][1]	Superiority P-value [2]
180 Days Late Loss, In-stent (mm)	0.10± 0.23 (23)	0.85± 0.36 (27)	-0.76 [-0.93, -0.59] [1]	< 0.0001

Note: N is the number of subjects.
[1]By normal approximation
[2]One-tailed p-value by t-test, to be compared to a 5% significance level

Table 9.3-2: SPIRIT FIRST Clinical Results

	OUTCOMES AT 6 MONTHS[1]			OUTCOMES AT 3 YEARS[1] (latest available follow-up)		
	XIENCE V (N = 27)	VISION (N = 29)	Difference [95% CI][2]	XIENCE V (N = 27)	VISION (N = 29)	Difference [95% CI][2]
COMPOSITE EFFICACY & SAFETY						
TVF[3]	7.7% (2/26)	21.4% (6/28)	-13.74% [Assump. not met]]	15.4% (4/26)	32.1% (9/28)	-16.76% [Assump. not met]
MACE[4]	7.7% (2/26)	21.4% (6/28)	-13.74% [Assump. not met]	15.4% (4/26)	25.0% (7/28)	-9.62% [Assump. not met]
EFFICACY						
Ischemia-Driven TLR	3.8% (1/26)	21.4% (6/28)	-17.58% [Assump. not met]	7.7% (2/26)	25.0% (7/28)	-17.31% [Assump. not met]
TLR, CABG	0.0% (0/26)	3.6% (1/28)	-3.57% [Assump. not met]	0.0% (0/26)	3.6% (1/28)	-3.57% [Assump. not met]
TLR, PCI	3.8% (1/26)	17.9% (5/28)	-14.01% [Assump. not met]	7.7% (2/26)	21.4% (6/28)	-13.74% [Assump. not met]
Ischemia-Driven non-TLR TVR	0.0% (0/26)	0.0% (0/28)	0.00% [Assump. not met]	0.0% (0/26)	10.7% (3/28)	-10.71% [Assump. not met]
non-TLR TVR, CABG	0.0% (0/26)	0.0% (0/28)	0.00% [Assump. not met]	0.0% (0/26)	3.6% (1/28)	-3.57% [Assump. not met]
non-TLR TVR, PCI	0.0% (0/26)	0.0% (0/28)	0.00% [Assump. not met]	0.0% (0/26)	7.1% (2/28)	-7.14% [Assump. not met]
SAFETY						
All Death	0.0% (0/26)	0.0% (0/28)	0.00% [Assump. not met]	0.0% (0/26)	0.0% (0/28)	0.00% [Assump. not met]
Cardiac Death	0.0% (0/26)	0.0% (0/28)	0.00% [Assump. not met]	0.0% (0/26)	0.0% (0/28)	0.00% [Assump. not met]
Non-Cardiac Death	0.0% (0/26)	0.0% (0/28)	0.00% [Assump. not met]	0.0% (0/26)	0.0% (0/28)	0.00% [Assump. not met]
MI	3.8% (1/26)	0.0% (0/28)	3.85% [Assump. not met]	7.7% (2/26)	0.0% (0/28)	7.69% [Assump. not met]
QMI	3.8% (1/26)	0.0% (0/28)	3.85% [Assump. not met]	3.8% (1/26)	0.0% (0/28)	3.85% [Assump. not met]
NQMI	0.0% (0/26)	0.0% (0/28)	0.00% [Assump. not met]	3.8% (1/26)	0.0% (0/28)	3.85% [Assump. not met]
Cardiac Death or MI	3.8% (1/26)	0.0% (0/28)	3.85% [Assump. not met]	7.7% (2/26)	0.0% (0/28)	7.69% [Assump. not met]
Stent Thrombosis – Protocol defined	0.0% (0/26)	0.0% (0/28)	0.00% [Assump. not met]	0.0% (0/26)	0.0% (0/28)	0.00% [Assump. not met]
Acute (< 1 day)	0.0% (0/27)	0.0% (0/29)	0.00% [Assump. not met]	0.0% (0/27)	0.0% (0/29)	0.00% [Assump. not met]
Subacute (1 – 30 days)	0.0% (0/27)	0.0% (0/29)	0.00% [Assump. not met]	0.0% (0/27)	0.0% (0/29)	0.00% [Assump. not met]
Late (> 30 days)	0.0% (0/26)	0.0% (0/28)	0.00% [Assump. not met]	0.0% (0/26)	0.0% (0/28)	0.00% [Assump. not met]

Note:

- Assump. not met means that assumption of normal approximation not met due to small sample size or frequency of events.

[1] 6 month and 3 year time frames include follow-up window (180 +14 days and 1095 + 28 days) respectively.

[2] Confidence Interval was calculated using the normal approximation, not adjusted for multiplicity and is meant for descriptive purposes only.

[3] TVF is defined as a hierarchical composite of cardiac death, MI, ischemic-driven TLR and ischemic-driven non-TLR TVR.

[4] MACE is defined as a hierarchical composite of cardiac death, MI, ischemic-driven TLR.

Table 9.3-3: SPIRIT FIRST 180-Day Angiographic and IVUS Results

	XIENCE V (N = 27)	VISION (N = 29)	Difference [95% CI][1]
ANGIOGRAPHIC RESULTS			
In-Stent MLD			
Post-Procedure	2.34± 0.26 (27)	2.43± 0.30 (29)	-0.09 [-0.24, 0.06]
6 Months	2.28± 0.33 (23)	1.58± 0.41 (27)	0.70 [0.49,0.91]
In-Segment MLD			
Post-Procedure	2.07± 0.37 (27)	2.15± 0.37 (29)	-0.08 [-0.28, 0.12,]
6 Months	2.04 ± 0.40 (23)	1.54± 0.41 (27)	0.50 [0.27, 0.73]
In-Stent %DS			
Post-Procedure	12.34 ± 4.02 (27)	14.85 ± 4.76 (29)	-2.51 [-4.87, -0.16]
6 Months	15.57 ± 7.64 (23)	38.61 ± 14.25 (27)	-23.05 [-29.45, -16.64]
In-Segment %DS			
Post-Procedure	20.82 ± 7.65 (27)	23.14 ± 8.03% (29)	-2.32 [-6.52, 1.88]
6 Months	21.89 ± 11.15 (23)	40.78 ± 13.67 (27)	-18.89 [-25.95,-11.83]
Late Loss			
In-Stent	0.10 ± 0.23 (23)	0.85 ± 0.36 (27)	-0.76 [-0.93, -0.59]
In-Segment	0.09 ± 0.20 (23)	0.61 ± 0.37 (27)	-0.53 [-0.69, -0.36]
Binary Restenosis			
In-Stent	0.0% (0/23)	25.9% (7/27)	-25.93% [Assump. not met]
In-Segment	4.3% (1/23)	33.3% (9/27)	-28.99% [Assump. not met]
IVUS RESULTS			
Neointimal Volume (mm^3)	10.29± 13.32 (21)	38.29± 19.08 (24)	-28.00 [-37.82, -18.19]
% Volume Obstruction	7.95± 10.44 (21)	28.11± 13.98 (24)	-20.16 [-27.53, -12.79]
Incomplete Apposition			
Post Procedure	0.0% (0/ 27)	10.7% (3/ 28)	-10.71% [Assump. not met]
6 month	0.0% (0/ 21)	0.0% (0/ 22)	0.00% [Assump. not met]
Persistent	0.0% (0/ 27)	0.0% (0/ 28)	0.00% [Assump. not met]
Late Acquired	0.0% (0/ 21)	0.0% (0/ 22)	0.00% [Assump. not met]

Note:

- Assump. not met means that assumption of normal approximation not met due to small sample size or frequency of events.

[1]Confidence Interval was calculated using the normal approximation, not adjusted for multiplicity and is meant for descriptive purposes only.

Table 9.3-4: SPIRIT FIRST ARC defined Definite+Probable Stent Thrombosis Through 3 Years

	XIENCE V (N=27)	VISION (N=29)	Difference [95% CI][1]
ARC Definite+Probable Stent Thrombosis (0 days – 3 years)	0.0% (0/26)	0.0% (0/28)	0.00% [Assump. not met]
Acute (< 1 day)	0.0% (0/27)	0.0% (0/28)	0.00% [Assump. not met]
Subacute (1 – 30 days)	0.0% (0/27)	0.0% (0/28)	0.00% [Assump. not met]
Late (31 days – 1 year)	0.0% (0/26)	0.0% (0/28)	0.00% [Assump. not met]
Very Late (1 – 3 years)	0.0% (0/26)	0.0% (0/28)	0.00% [Assump. not met]

Note:
- Assump. not met means that assumption of normal approximation not met due to small sample size or frequency of events.

[1] Confidence Interval was calculated using the normal approximation, not adjusted for multiplicity and is meant for descriptive purposes only.

9.4 SPIRIT II AND SPIRIT III POOLED ANALYSIS

In order to better estimate the incidence of low frequency events or outcomes in various specific subject subgroups, a subject-level pooled analysis was conducted of both randomized trials comparing the XIENCE V stent versus the TAXUS stent. Data from the SPIRIT II and SPIRIT III clinical trials were pooled to compare the XIENCE V stent to the TAXUS control stent in 1302 subjects out to 1 year (393 days) of follow-up. These two studies have subjects with similar baseline and angiographic characteristics and the key elements of study design including inclusion and exclusion criteria and endpoint definitions are comparable. The subject level data were included until the latest available time point of 1 year for each trial. Table 9.4-1 shows the subject disposition over time for the SPIRIT II and III RCT. The percentage of the total number of subjects that were enrolled in the studies and completed their 1 year follow-up was 96.5%.

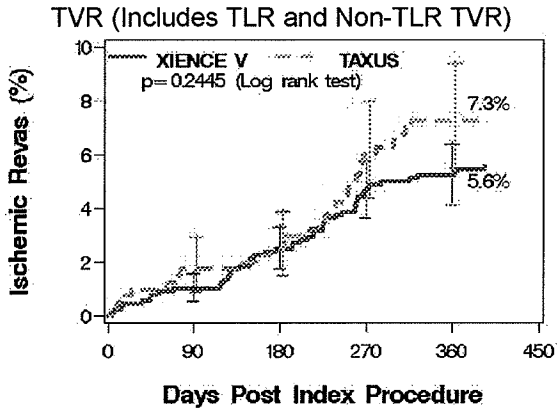
Table 9.4-1: Subject Disposition Table (N=1302; SPIRIT II and SPIRIT III RCT)

	30-Day Follow-up		9-Month Follow-up		1-Year Follow-up	
	XIENCE V (890)		XIENCE V (873)		XIENCE V (866)	
	SPIRIT II	SPIRIT III	SPIRIT II	SPIRIT III	SPIRIT II	SPIRIT III
Subjects	223	667	220	653	220	646
	TAXUS (407)		TAXUS (395)		TAXUS (392)	
	SPIRIT II	SPIRIT III	SPIRIT II	SPIRIT III	SPIRIT II	SPIRIT III
Subjects	77	330	76	319	76	316

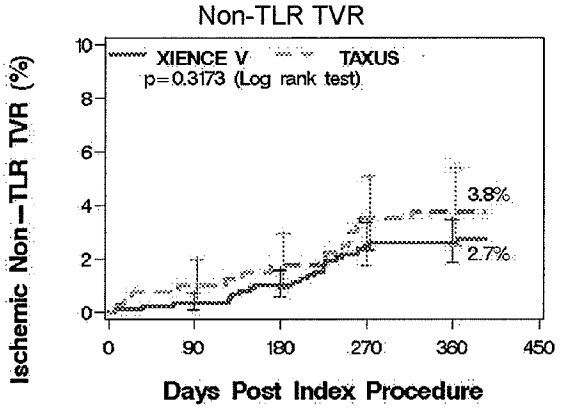
It is acknowledged that these retrospective pooled analyses are exploratory and hypothesis-generating. Definitive proof of the presence or absence of any differences between such sub-groups requires prospectively powered assessment in dedicated clinical trials. The pooled analysis from SPIRIT II and SPIRIT III trials includes subjects from single-blind trials with similar inclusion and exclusion criteria in 1,302 subjects with 1,506 lesions.

As shown in Figure 9.4-1, at one year, the analyses of pooled trials suggest a reduction in the rates of TVR and TLR for the XIENCE V stent compared to the TAXUS stent through one year. All CI bars represent a 1.5 standard error.

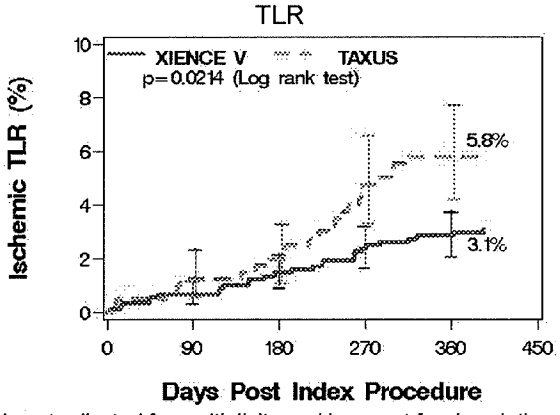
Figure 9.4-1: Kaplan Meier Hazard Curves for Time to First TVR or TLR Event through 393 Days (Pooled SPIRIT II and SPIRIT III RCTs)



Note: P-value is not adjusted for multiplicity and is meant for descriptive purposes only.



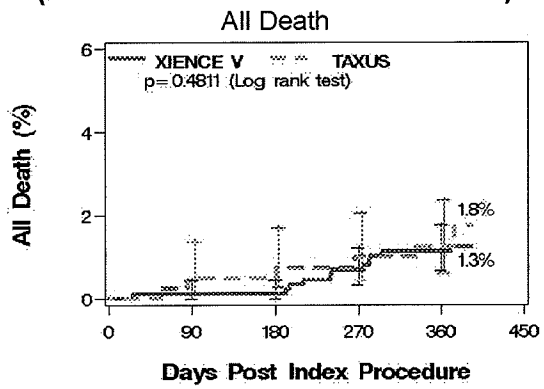
Note: P-value is not adjusted for multiplicity and is meant for descriptive purposes only.



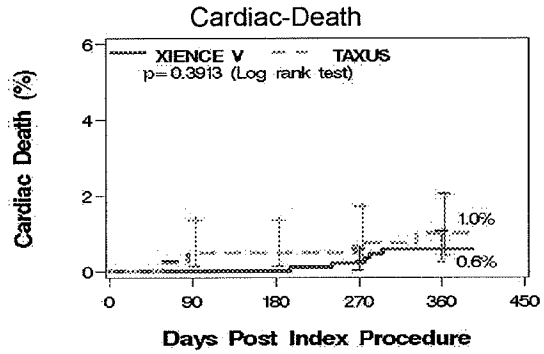
Note: P-value is not adjusted for multiplicity and is meant for descriptive purposes only.

Pooled analyses of the rates of all death, cardiac death, and non-cardiac death through 1 year are shown in Figure 9.4-2.

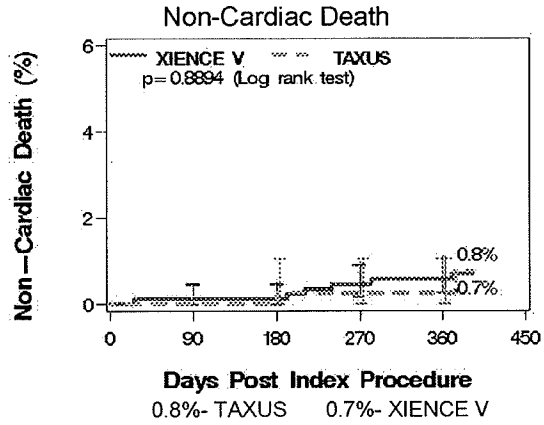
Figure 9.4-2: Kaplan Meier Hazard Curves for Time to Death through 393 Days (Pooled SPIRIT II and SPIRIT III RCTs)



Note: P-value is not adjusted for multiplicity and is meant for descriptive purposes only.



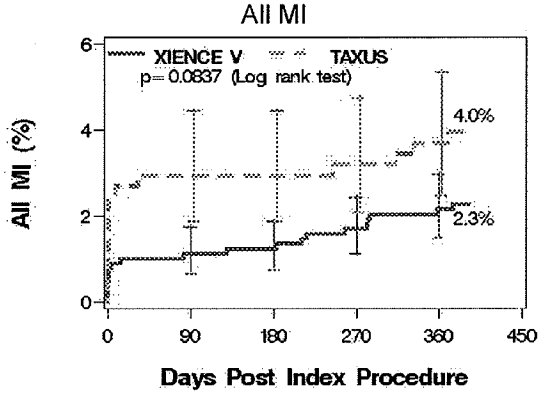
Note: P-value is not adjusted for multiplicity and is meant for descriptive purposes only.



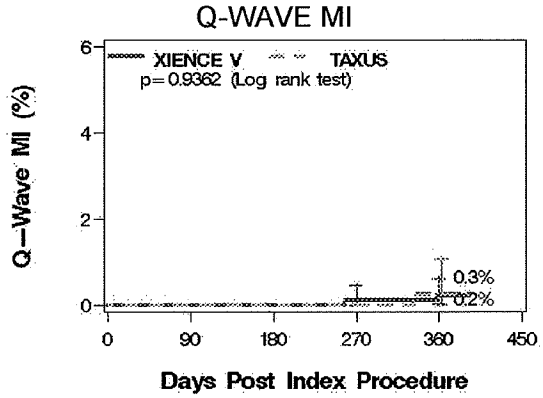
Note: P-value is not adjusted for multiplicity and is meant for descriptive purposes only.

Pooled analyses of the rates of MIs through 1 year are shown in Figure 9.4-3.

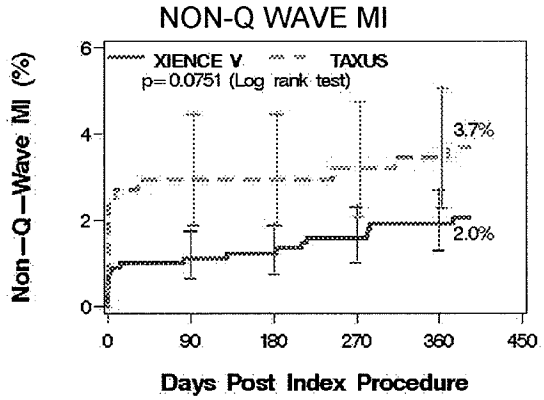
Figure 9.4-3: Kaplan Meier Hazard Curves for Time to First MI Event through 393 Days (Pooled SPIRIT II and SPIRIT III RCTs)



Note: P-value is not adjusted for multiplicity and is meant for descriptive purposes only.



Note: P-value is not adjusted for multiplicity and is meant for descriptive purposes only.



Note: P-value is not adjusted for multiplicity and is meant for descriptive purposes only.

9.4.1 Stent Thrombosis in SPIRIT II and SPIRIT III Pooled Analysis

The results for the pooled analysis rates of stent thrombosis at one year are shown below in Figure 9.4.1-1. Rates were low for both treatments in this pooled analysis and consistent with the published literature[10]. The rates of stent thrombosis were evaluated based on the SPIRIT II and III protocol defined definition and the ARC definition for definite + probable thrombosis (see definitions above in Section 8.2). These data are presented in table 9.4.1-1.

Table 9.4.1-1 Pooled Results for Stent Thrombosis through 1 year (SPIRIT II and SPIRIT III RCT)

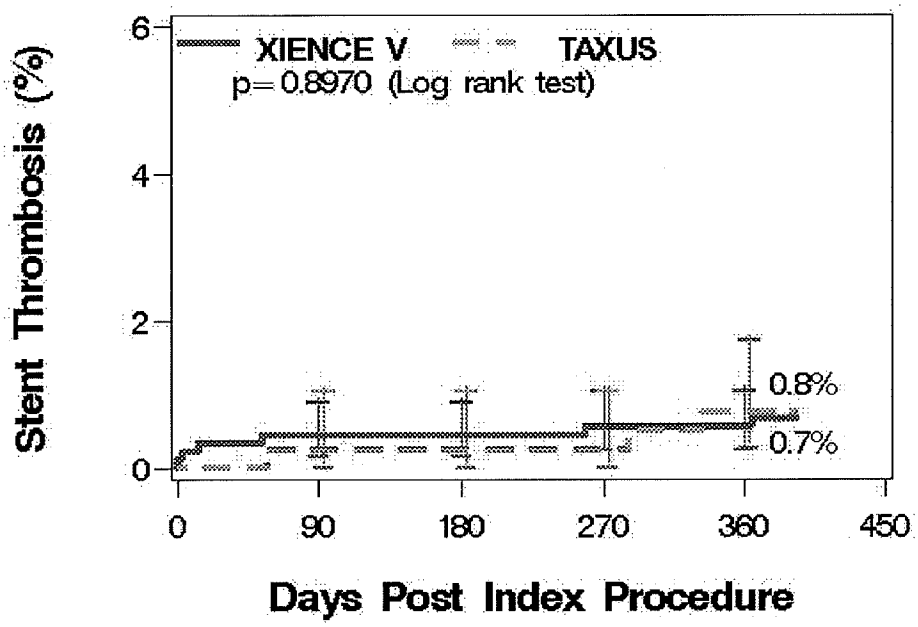
	XIENCE V (N=892)	95% CI[1]	TAXUS (N=410)	95% CI[1]
0 - 30 days				
Protocol	0.3% (3/890)	[0.07%, 0.98%]	0.0% (0/407)	[0.00%, 0.90%]
ARC (definite + probable)	0.4% (4/890)	[0.12%, 1.15%]	0.2% (1/407)	[0.01%, 1.36%]
31 days – 1 year				
Protocol	0.3% (3/866)	[0.07%, 1.01%]	0.8% (3/394)	[0.16%, 2.21%]
ARC (definite + probable)	0.3% (3/867)	[0.07%, 1.01%]	0.8% (3/394)	[0.16%, 2.21%]
0 – 1 year				
Protocol	0.7% (6/867)	[0.25%, 1.50%]	0.8% (3/394)	[0.16%, 2.21%]
ARC (definite + probable)	0.8% (7/868)	[0.32%, 1.65%]	0.8% (3/394)	[0.16%, 2.21%]

Note: timeframe for 1 year includes the follow-up window (365 + 28 days).
[1] By Clopper-Pearson Exact Confidence Interval

[10] Ellis SG CA, Grube E, Popma J, Koglin J, Dawkins KD, Stone GW. Incidence, timing, and correlates of stent thrombosis with the polymeric paclitaxel drug-eluting stent: a TAXUS II, IV, V, and VI meta-analysis of 3,445 patients followed for up to 3 years. *J Am Coll Cardiol.* 2007;49:1043-1051.

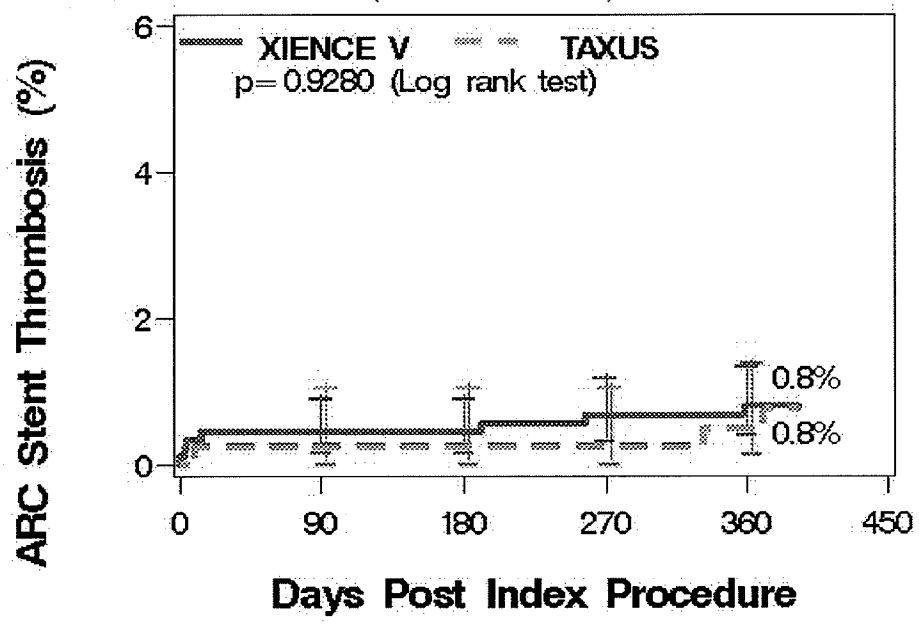
Figure 9.4.1-1: Kaplan Meier Hazard Curves for Time to First Stent Thrombosis Event through 393 Days (Pooled SPIRIT II and SPIRIT III RCTs)

Protocol Defined Stent Thrombosis



Note: P-value is not adjusted for multiplicity and is meant for descriptive purposes only.

ARC Defined Stent Thrombosis (Definite + Probable)



Note: P-value is not adjusted for multiplicity and is meant for descriptive purposes only.

9.4.2 Diabetics in SPIRIT II and SPIRIT III Pooled Analysis

Diabetic subjects comprise an important subject subgroup that is at increased risk for cardiovascular morbidity and mortality. Although diabetic subjects were included in the SPIRIT family of trials, there were no pre-specified hypotheses or trial features that warrant a specific labeled indication for the use of the XIENCE V stent in diabetic individuals.

Table 9.4.2-1 shows the clinical outcomes through 1 year in subjects pooled from SPRIT II and III. The randomization was stratified by history of diabetes to assure a balance between the XIENCE V and TAXUS treatment arms. In XIENCE V patients, there were numerically higher event rates in diabetics compared with non-diabetics. The event rates for TAXUS in diabetics were lower than the event rates for TAXUS non-diabetics. Given the relatively small sample size of the diabetic population and potential for confounding variables, no conclusions can be drawn from these post-hoc analyses.

Table 9.4.2-1: Clinical Results in Diabetics and Non-Diabetics through 1 year (SPIRIT II and SPIRIT III RCT Pooled Population)

	Non-Diabetics XIENCE V (N=643)	Non-Diabetics TAXUS (N=296)	All Diabetics XIENCE V (N=249)	All Diabetics TAXUS (N=110)
TLR	2.5% (16/629)	7.6% (22/290)	4.5% (11/244)	1.0% (1/104)
TVR(CABG/PCI), non TL	2.5% (16/629)	4.1% (12/290)	3.3% (8/244)	2.9% (3/104)
All Death	1.0% (6/631)	2.4% (7/291)	2.0% (5/246)	0.0% (0/104)
Cardiac Death	0.3% (2/631)	1.4% (4/291)	1.2% (3/246)	0.0% (0/104)
Non-Cardiac Death	0.6%(4/631)	1.0%(3/291)	0.8%(2/246)	0.0% (0/104)
MI	1.4% (9/629)	4.5% (13/290)	4.5% (11/244)	2.9% (3/104)
Cardiac Death or MI	1.7% (11/629)	5.2% (15/290)	5.3% (13/244)	2.9% (3/104)
Stent Thrombosis				
Protocol defined	0.5% (3/627)	1.0% (3/287)	1.3% (3/240)	0.0% (0/104)
ARC definite + probable	0.3% (2/627)	0.7% (2/287)	2.1% (5/241)	1.0% (1/104)

Table 9.4.2-2: Clinical Results in Diabetics through 1 year (SPIRIT II and SPIRIT III RCT Pooled Population – XIENCE V Subjects)

	Non-Diabetics (N=643)	All Diabetics (N=249)	Insulin-Dependent Diabetics (N=63)	Non-Insulin-Dependent Diabetics (N=186)
TLR	2.5% (16/629)	4.5% (11/244)	6.5% (4/62)	3.8% (7/182)
TVR(CABG/PCI), non TL	2.5% (16/629)	3.3% (8/244)	1.6% (1/62)	3.8% (7/182)
All Death	1.0% (6/631)	2.0% (5/246)	3.2% (2/63)	1.6% (3/183)
Cardiac Death	0.3% (2/631)	1.2% (3/246)	1.6% (1/63)	1.1% (2/183)
Non-Cardiac Death	0.6% (4/631)	0.8%(2/246)	1.6% (1/63)	0.5% (1/183)
MI	1.4% (9/629)	4.5% (11/244)	9.7% (6/62)	2.7% (5/182)
Cardiac Death or MI	1.7% (11/629)	5.3% (13/244)	9.7% (6/62)	3.8% (7/182)
Stent Thrombosis				
Protocol defined	0.5% (3/627)	1.3% (3/240)	1.6% (1/61)	1.1% (2/179)
ARC definite + probable	0.3% (2/627)	2.1% (5/241)	1.6% (1/61)	2.2% (4/180)

9.4.3 Dual Vessel treatment in SPIRIT II and SPIRIT III Pooled Analysis

Subjects requiring treatment in more than one vessel comprise a subgroup that is at increased risk for cardiovascular events compared with single vessel disease patients. Although subjects requiring both single and dual vessel treatment were included in the SPIRIT family of trials,

there were no pre-specified hypothesis or trial features that warrant a specific labeled indication for the use of the XIENCE V stent in dual vessel individuals.

Table 9.4.3-1 shows the clinical outcomes through 1 year in subjects pooled from SPRIT II and III. The randomization was stratified by the number of vessels treated to assure a balance between the XIENCE V and TAXUS treatment arms. Numerically lower event rates were observed for XIENCE V and TAXUS in single compared to dual vessel treatment. However, given the small sample size for dual vessel treatment, no conclusions can be drawn from this post-hoc analysis.

Table 9.4.3-1: Clinical Results in Single and Dual Vessel Treatment through 1 year (SPIRIT II and SPIRIT III RCT Pooled Population)

	Single Vessel XIENCE V (N=752)	Single Vessel TAXUS (N=344)	Dual Vessel XIENCE V (N=140)	Dual Vessel TAXUS (N=65)
TLR	2.9% (21/735)	4.5% (15/333)	4.3% (6/138)	12.5% (8/64)
TVR(CABG/PCI), non TL	2.3% (17/735)	2.1% (7/333)	5.1% (7/138)	12.5% (8/64)
All Death	1.5% (11/739)	1.2% (4/333)	0.0% (0/138)	4.6% (3/65)
Cardiac Death	0.7% (5/739)	0.6% (2/333)	0.0% (0/138)	3.1% (2/65)
Non-Cardiac Death	0.8% (6/739)	0.6% (2/333)	0.0% (0/138)	1.5% (1/65)
MI	1.9% (14/735)	3.0% (10/333)	4.3% (6/138)	9.4% (6/64)
Cardiac Death or MI	2.4% (18/735)	3.3% (11/333)	4.3% (6/138)	10.9% (7/64)
Stent Thrombosis				
Protocol defined	0.3% (2/729)	0.6% (2/332)	2.9% (4/138)	1.6% (1/62)
ARC definite + probable (TLR not censored)	0.5% (4/730)	0.6% (2/332)	2.2% (3/138)	1.6% (1/62)

10.0 INDIVIDUALIZATION OF TREATMENT

The risks and benefits should be considered for each patient before using the XIENCE V stent. Patient selection factors to be assessed should include a judgment regarding risk of long-term antiplatelet therapy. Stenting is generally avoided in those patients at a heightened risk of bleeding (e.g., patients with recently active gastritis or peptic ulcer disease) in which anticoagulation therapy would be contraindicated.

Antiplatelet drugs should be used in combination with the XIENCE V stent. Physicians should use information from the SPIRIT Clinical trials, coupled with current drug eluting stent (DES) literature and the specific needs of individual patients to determine the specific antiplatelet/anticoagulation regimen to be used for their patients in general practice. See also 5.2 – Precautions, Pre- and Post-Procedure Antiplatelet Regimen, Section 5.6 – Precautions, Use in Special Populations and Section 5.7 – Precautions, Lesion/Vessel Characteristics.

Premorbid conditions that increase the risk of poor initial results or the risks of emergency referral for bypass surgery (diabetes mellitus, renal failure, and severe obesity) should be reviewed.

11.0 PATIENT COUNSELING AND PATIENT INFORMATION

Physicians should consider the following in counseling patients about this product:

- Discuss the risks associated with stent placement.
- Discuss the risks associated with an everolimus-eluting stent.
- Discuss the risks of early discontinuation of the antiplatelet therapy.
- Discuss the risks of late stent thrombosis with DES use in higher risk patient subgroups.
- Discuss the risk/benefit issues for this particular patient.
- Discuss alteration to current life-style immediately following the procedure and over the long term.

The following patient materials are available for this product:

- A Patient Information Guide which includes information on coronary artery disease, the implant procedure and the XIENCE V Everolimus Eluting Coronary Stent System (provided to physician, on-line at www.XIENCEV.com/PatientGuide, or by calling customer service 1-800-227-9902).
- A Stent Implant Card that includes both patient information and stent implant information (provided in package)

12.0 HOW SUPPLIED

Sterile: This device is sterilized with ethylene oxide gas, non-pyrogenic. It is intended for single use only. Do not resterilize. Do not use if the package is opened or damaged.

Contents: One (1) XIENCE V Everolimus Eluting Coronary Stent System, one (1) Flushing tool, (for the XIENCE V EECSS Rapid Exchange (RX) Stent System), one (1) Stent Implant Card, one (1) Patient Information Guide.

Storage: Store in a dry, dark, cool place. Protect from light. Do not remove from carton until ready for use. Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

13.0 OPERATOR'S INSTRUCTIONS

13.1 Inspection Prior to Use

- Carefully inspect the sterile package before opening and check for damage to the sterile barrier. Do not use if the integrity of the sterile package has been compromised.
- Do not use after the "Use By" date.
- Tear open the foil pouch and remove the inner pouch. **Note: the outside of the inner pouch is NOT sterile.** Open the inner pouch and pass or drop the product into the sterile field using an aseptic technique.
- Prior to using the XIENCE V Everolimus Eluting Coronary Stent System, carefully remove the system from the package and inspect for bends, kinks, and other damage. Verify that the stent does not extend beyond the radiopaque balloon markers. Do not

use if any defects are noted. However, **do not manipulate, touch, or handle the stent** with your fingers, which may cause coating damage, contamination or stent dislodgement from the delivery balloon.

Note: At any time during use of the XIENCE V Rapid Exchange (RX) EECSS, if the stainless steel proximal shaft has been bent or kinked, do not continue to use the catheter.

13.2 Materials Required

- Appropriate guiding catheter(s). See Table 1-1, XIENCE V Stent System Product Description
- 2 – 3 syringes (10 – 20 ml)
- 1,000 u/500 ml Heparinized Normal Saline (HepNS)
- 0.014 inch (0.36 mm) x 175 cm (minimum length) guide wire
- Rotating hemostatic valve with appropriate minimum inner diameter [0.096 inch (2.44 mm)]
- 60% contrast diluted 1:1 with heparinized normal saline
- Inflation device
- Pre-deployment dilatation catheter
- Three-way stopcock
- Torque device
- Guide wire introducer
- Appropriate arterial sheath
- Appropriate anticoagulation and antiplatelet drugs

13.3 Preparation

13.3.1 Packaging Removal

Note: The foil pouch is not a sterile barrier. The inner header bag (pouch) within the foil pouch is the sterile barrier. Only the contents of the inner pouch should be considered sterile. The outside surface of the inner pouch is NOT sterile.

1. Carefully remove the delivery system from its protective tubing for preparation of the delivery system. When using a Rapid Exchange (RX) system, do not bend or kink the hypotube during removal.

2. Remove the product mandrel and protective stent sheath by grasping the catheter just proximal to the stent (at the proximal balloon bond site), and with the other hand, grasp the stent protector and gently remove distally. If unusual resistance is felt during product mandrel and stent sheath removal, do not use this product and replace with another. Follow product returns procedure for the unused device.

13.3.2 Guide Wire Lumen Flush

1. Over the Wire (OTW) only: Flush the guide wire lumen with HepNS until fluid exits the distal end of the delivery system.

2. Rapid Exchange (RX) only: Flush the guide wire lumen with HepNS using the flushing tool supplied with the product. Insert the flushing tool into the tip of the catheter and flush until fluid exits the guide wire exit notch.

Note: Avoid manipulation of the stent while flushing the guide wire lumen, as this may disrupt the placement of the stent on the balloon.

13.3.3 Delivery System Preparation

1. Prepare an inflation device/syringe with diluted contrast medium.

2. Attach an inflation device/syringe to the stopcock; attach it to the inflation port of the product. Do not bend the product hypotube when connecting to the inflation device/syringe.

3. With the tip down, orient the delivery system vertically.

4. Open the stopcock to delivery system; pull negative for 30 seconds; release to neutral for contrast fill.

5. Close the stopcock to the delivery system; purge the inflation device/syringe of all air.

6. Repeat steps 3 through 5 until all air is expelled. If bubbles persist, do not use the product.

7. If a syringe was used, attach a prepared inflation device to stopcock.

8. Open the stopcock to the delivery system.

9. Leave on neutral

Note: If air is seen in the shaft, repeat *Delivery System Preparation* steps 3 through 5 to prevent uneven stent expansion.

13.4 Delivery Procedure

1. Prepare the vascular access site according to standard practice.

2. **Pre-dilate the lesion with a PTCA catheter of appropriate length and diameter for the vessel/lesion to be treated.** Limit the longitudinal length of pre-dilatation by the PTCA balloon to avoid creating a region of vessel injury that is outside the boundaries of the XIENCE V Stent.

Note: The labeled stent diameter refers to expanded stent inner diameter.

3. Maintain neutral pressure on the inflation device attached to the delivery system. Open the rotating hemostatic valve as wide as possible.

4. Backload the delivery system onto the proximal portion of the guide wire while maintaining guide wire position across the target lesion.

5. Carefully advance the delivery system into the guiding catheter and over the guide wire to the target lesion. When using a Rapid Exchange (RX) system be sure to keep the hypotube straight. Ensure guiding catheter stability before advancing the stent system into the coronary artery.

Note: If unusual resistance is felt before the stent exits the guiding catheter, do not force passage. Resistance may indicate a problem and the use of excessive force may result in stent damage or dislodgement. Maintain guide wire placement across the lesion and remove the delivery system and guiding catheter as a single unit.

6. Advance the delivery system over the guide wire to the target lesion under direct fluoroscopic visualization. Utilize the radiopaque balloon markers to position the stent across the lesion. Perform angiography to confirm stent position. If the position of the stent is not optimal, it should be carefully repositioned or removed (see Section 5.14 – Precautions, Delivery System Removal). The balloon markers indicate both the stent edges and the balloon shoulders. Expansion of the stent should not be undertaken if the stent is not properly positioned in the target lesion.

Note: Should **any resistance** be felt **at any time** during either lesion access or removal of the delivery system post-stent implantation, **remove the entire system as a single unit.** See Section 5.14 – Precautions, Delivery System Removal for specific delivery system removal instructions.

7. Tighten the rotating hemostatic valve. The stent is now ready to be deployed.

13.5 Deployment Procedure

CAUTION: Refer to Table 14-1: Typical XIENCE V Stent Compliance for *in vitro* stent inner diameter, nominal pressure, and RBP.

1. Prior to deployment, reconfirm the correct position of the stent relative to the target lesion using the radiopaque balloon markers.

2. Deploy the stent slowly by pressurizing the delivery system in 2 atm increments, every 5 seconds, until stent is completely expanded. Accepted practice generally targets an initial deployment pressure that would achieve a stent inner diameter ratio of about 1.1 times the reference vessel diameter (see Table 14-1). Maintain pressure for 30 seconds. If necessary, the delivery system can be repressurized or further pressurized to assure complete apposition of the stent to the artery wall. **Do not exceed the labeled rated burst pressure (RBP) of 16 atm (1.62 MPa).**

3. Fully cover the entire lesion and balloon treated area (including dissections) with the XIENCE V stent, allowing for adequate stent coverage into healthy tissue proximal and distal to the lesion.

4. Deflate the balloon by pulling negative on the inflation device for 30 seconds. Confirm complete balloon deflation before attempting to move the delivery system. If unusual resistance is felt during stent delivery system withdrawal, pay particular attention to guiding catheter position.

5. Confirm stent position and deployment using standard angiographic techniques. For optimal results, the entire stenosed arterial segment should be covered by the stent. Fluoroscopic visualization during stent expansion should be used in order to properly judge the optimum expanded stent diameter as compared to the proximal and distal coronary artery diameter(s). Optimal expansion requires that the stent be in full contact with the artery wall. Stent wall contact should be verified through routine angiography or intravascular ultrasound (IVUS).

6. If the deployed stent size is still inadequate with respect to reference vessel diameter, a larger balloon may be used to further expand the stent. If the initial angiographic appearance is sub-optimal, the stent may be further expanded using a low profile, high pressure, non-compliant balloon dilatation catheter. If this is required, the stented segment should be carefully recrossed with a prolapsed guide wire to avoid disrupting the stent geometry. Deployed stents should not be left under-dilated.

CAUTION: Do not dilate the stent beyond the following limits.

Nominal Stent Diameter	Dilatation Limit
2.5 mm to 3.0 mm	**3.5 mm**
3.5 mm to 4.0 mm	**4.5 mm**

7. If more than one XIENCE V stent is needed to cover the lesion and balloon

treated area, it is suggested that, to avoid the potential for gap restenosis, the stents be adequately overlapped. To ensure that there are no gaps between stents the balloon marker bands of the second XIENCE V stent should be positioned inside the deployed stent prior to expansion.

8. Reconfirm stent position and angiographic results. Repeat inflations until optimal stent deployment is achieved.

13.6 Removal Procedure

1. Deflate the balloon by pulling negative pressure on the inflation device for 30 seconds. Confirm complete balloon deflation before attempting to move the delivery system. If unusual resistance is felt during stent delivery system withdrawal, pay particular attention to the guiding catheter position.

2. Fully open the rotating hemostatic valve.

3. While maintaining the guide wire position and negative pressure on the inflation device, withdraw the delivery system.

Note: Should **any resistance** be felt **at any time** during either lesion access or removal of the delivery system post-stent implantation, the entire system should be **removed as a single unit.** See Section 5.14 – Precautions, Delivery System Removal for specific delivery system removal instructions.

4. Tighten the rotating hemostatic valve.

5. Repeat angiography to assess the stented area. If post-dilatation is necessary, ensure that the final stent diameter matches the reference vessel diameter. **Assure that the stent is not under-dilated.**

13.7 Post-Deployment Dilatation of Stent Segments

1. All efforts should be taken to assure that the stent is not underdilated. If the deployed stent size is still inadequate with respect to the vessel diameter, or if full contact with the vessel wall is not achieved, a larger balloon may be used to expand the stent further. The stent may be further expanded using a low profile, high pressure, and non-compliant balloon catheter. If this is required, the stented segment should be recrossed carefully with a prolapsed guide wire to avoid dislodging the stent. The balloon should be centered within the stent and should not extend outside of the stented region.

CAUTION: Do not dilate the stent beyond the following limits.

Nominal Stent Diameter	Dilatation Limit
2.5 mm to 3.0 mm	**3.5 mm**
3.5 mm to 4.0 mm	**4.5 mm**

14.0 *IN VITRO* COMPLIANCE INFORMATION

Table 14-1: Typical XIENCE V Stent Compliance
Nominal pressure for each diameter indicated by bold font.

Pressure		Stent ID (mm) by System Size				
(atm)	(MPa)	2.5 mm	2.75 mm	3.0 mm	3.5 mm	4.0 mm
8	0.81	**2.46**	**2.74**	2.90	3.46	3.86
9	0.91	2.52	2.81	**2.97**	**3.55**	**3.95**
10	1.01	2.58	2.87	3.04	3.63	4.03
11	1.11	2.63	2.92	3.10	3.69	4.10
12	1.22	2.68	2.97	3.15	3.75	4.17
13	1.32	2.72	3.01	3.19	3.80	4.23
14	1.42	2.75	3.05	3.23	3.84	4.28
15	1.52	2.78	3.08	3.26	3.89	4.33
16 (RBP)*	1.62	2.81	3.11	3.30	3.93	4.37
17	1.72	2.84	3.14	3.33	3.97	4.42
18	1.82	2.87	3.18	3.36	4.00	4.46

Note: These nominal data are based on *in vitro* testing at 37°C and do not take into account lesion resistance.
Ensure full deployment of the stent (see Section 13.5, Operator's Instructions, Deployment Procedure) and confirm the stent sizing angiographically.
*Do not exceed the rated burst pressure (RBP).

15.0 REUSE PRECAUTION STATEMENT

Do not use if sterile barrier is damaged. If damage is found call your Abbott Vascular, Cardiac Therapies representative.

For single patient use only. Do not reuse, reprocess or resterilize.

16.0 PATENTS

This product and/or its use are covered by one or more of the following United States patents: 5,040,548 ; 5,061,273 ; 5,154,725 ; 5,234,002 ; 5,242,396 ; 5,350,395 ; 5,451,233 ; 5,496,346 ; 5,514,154 ; 5,569,295 ; 5,603,721 ; 5,636,641 ; 5,649,952 ; 5,728,158 ; 5,735,893 ; 5,759,192 ; 5,780,807 ; 5,868,706 ; 6,056,776 ; 6,131,266 ; 6,179,810 ; 6,273,911 ; 6,309,412 ; 6,312,459 ; 6,369,355 ; 6,419,693 ; 6,432,133 ; 6,482,166 ; 6,485,511 ; 6,629,991 ; 6,629,994 ; 6,651,478 ; 6,656,220 ; 6,736,843 ; 6,746,423 ; 6,753,071 ; 6,818,247 ; 6,827,734 ; 6,887,219 ; 6,887,510 ; 6,890,318 ; 6,908,479 ; 6,921,411 ; 6,929,657 ; 6,939,373 ; 6,957,152. Other US patents pending. Foreign patents issued and pending.

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Graphical Symbols for Medical Device Labeling

Manufacturer	REF Catalogue Number	F French Size
Do not reuse, do not resterilize	STERILE EO Sterilized using Ethylene Oxide	Consult Instructions for Use
Use By	LOT Batch Code	Date of Manufacture
Guiding Catheter	Non-Pyrogenic	Contents (Numeral represents quantity of units inside)
Inner Diameter		